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GHB's Path to Legitimacy: An Administrative and Legislative History of Xyrem

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Abstract

This paper traces the path of a chemical compound (gamma-hydroxybutyrate, or GHB) from its status as an abused street drug to that of a legitimate, life-altering prescription treatment for a debilitating condition. It is the story of the public and private sectors working hand-in-hand to both protect the public from the detrimental effects of abuse while simultaneously ensuring that the thousands of Americans who need treatment are able to get it. It is also the story of an administrative and legislative system which, at least in this instance, seems to have worked to almost everyone's satisfaction, despite the number of competing interests that were at stake.

At the same time, this paper does not attempt to explain or evaluate medical claims about GHB or Xyrem. Instead, it is a historical account of the administrative and legislative path that led to GHB's approval as a treatment for cataplexy related to narcolepsy. However, the paper does not take a linear approach to GHB's history; instead the administrative and legislative processes are treated separately. Although the processes influenced each other in a myriad of ways, they were also distinct enough to require separate discussion. The story of Congress' unprecedented bifurcated scheduling was surely a result, in part, of the success of Orphan's clinical trials and pending New Drug Application ("NDA"), and the NDA was only allowed to go forward because of the bifurcated scheduling. Yet, to completely integrate the two stories would be needlessly confusing to the reader.

(Samantha Reid) and two friends, none of them yet 16, were at a party given by a 25 year-old man in Woodhaven, Michigan. Samantha Reid drank a Mountain Dew—a soft drink—and passed out within minutes. She vomited in her sleep, and she died. Her friend, Melanie Sindone, also 15, passed out as well. Melanie lapsed into a coma, but she has survived.

These two girls had no reason to believe that they were drinking anything dangerous. But they were wrong. Their drinks had been laced with the drug GHB, commonly known as a date rape drug.” Samantha was undoubtedly slipped it for the purpose that this name suggests, although she died before that purpose was accomplished.

... GHB and its analogues are becoming increasingly common in our nation. They are finding their way into nightclubs, onto campuses and into homes. They are being used by sexual predators against young—sometimes very young—women. Their unwitting victims may be raped, become violently ill, and even die.”

- Spencer Abraham, United States Senator¹

“My cataplexy caused numerous daily episodes of complete body collapse, such that I couldn’t leave my office or home without risk of harm to myself or others. Feeling any emotion, humor, anger or mere enthusiasm, would result in sudden immediate collapse. . . My best description of the sudden collapse of cataplexy would be to imagine a puppet on strings and suddenly the strings, which are your muscle tone, are immediately let go and so you fall to the ground immediately, and your head comes down last and whips against whatever – sidewalk or table corner or escalator or whatever might be there. I have been rescued by police and emergency squads and life guards and well-meaning strangers and friends. . . I do know others whose fall has occurred at the top of the stairs and they fell down backwards and killed themselves.

... In 1982 my treating physician sent me to Sunnybrook Medical Center in Toronto, Canada to begin prescriptive use of Xyrem. . . my severe cataplexy symptoms disappeared almost overnight.”

- Bob Cloud, narcolepsy/cataplexy patient²

²Bob Cloud, Testimony before the Food and Drug Administration Peripheral and Central Nervous System Drugs Advisory Committee (June 6, 2001) (transcript available at <http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3754t1.txt>).

Introduction

Narcolepsy is a rare disease that affects about 140,000 Americans, which is about .05% of the population.³ It is characterized by excessive daytime sleepiness, cataplexy, sleep paralysis, and hypnagogic hallucinations⁴ which may represent the outward manifestations of a disrupted sleep cycle.⁵ Cataplexy is the second most common form of narcolepsy and affects about 30%-50% of patients, or about 24,000 people.⁶ It is characterized by the loss of skeletal muscle tone without loss of consciousness.⁷ Attacks are frequently prompted by laughter, embarrassment, social interactions with strangers, sudden anger, athletic exertion or sexual intercourse.⁸ A cataplexy attack is different than the regular sleep attacks that affect most narcoleptics – instead of simply falling asleep, patients experience “bilateral skeletal muscle weakness.”⁹ “Partial cataplexy attacks may involve only certain muscle groups, resulting in head drooping or knee buckling; complete cataplexy attacks may involve total skeletal muscle atonia, resulting in collapse” accompanied by an inability to move.¹⁰ At the same time, while suffering a cataplexy attack, patients maintain all forms of consciousness, including the ability to hear, see, and understand what is happening around them.¹¹ Such a condition is clearly debilitating and frequent attacks can have a devastating effect on patient’s personal and professional lives.¹² They cannot sustain regular social interactions because the slightest change in emotion may trigger

³David E. Fuller and Carl S. Hornfeldt, *From Club Drug to Orphan Drug: Sodium Oxybate (Xyrem) for the Treatment of Cataplexy*, 23(9) PHARMACOTHERAPY 2003, 1205, 1205 (2003).

⁴Hypnagogic hallucinations are dreams that occur during the very early stages of sleep, when people feel as though they are still awake. Daniel DeNoon, *What Dreams May Come Come Not From Waking Memory*, WebMD, available at http://my.webmd.com/content/article/28/1728_62251.htm (Feb. 24, 2004).

⁵Fuller and Hornfeldt, *supra* note 3, at 1205.

⁶*Id.*; Dayton Reardon, Testimony before the Food and Drug Administration Peripheral and Central Nervous System Drugs Advisory Committee (June 6, 2001) (transcript available at <http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3754t1.txt>).

⁷Jerome Siegel, *Narcolepsy*, SCIENTIFIC AMERICAN, Jan. 2000, at 76

⁸*Id.*

⁹Fuller and Hornfeldt, *supra* note 3, at 1205.

¹⁰*Id.* at 1205-06

¹¹*Id.*

¹²See, e.g. Sharon Fitzgerald, Bob Cloud, Richard Gelula, Testimony before the Food and Drug Administration Peripheral and Central Nervous System Drugs Advisory Committee (June 6, 2001) (transcript available at

an attack, the mildest of which usually do not go unnoticed.¹³ Moreover, they face risks of injury upon collapse such as hitting one's head on hard surfaces or falling down a flight of stairs.¹⁴

There is no known cure for narcolepsy or cataplexy.¹⁵ While anti-depressants are sometimes prescribed off-label in order to treat cataplexy, this treatment is often unsatisfactory for patients because tolerance may develop and, upon sudden withdrawal of the drugs, the frequency and severity of cataplexy attacks sometimes increase.¹⁶ Orphan Medical, Inc. ("Orphan") has developed the "first and only FDA-approved medication for the treatment of cataplexy associated with narcolepsy."¹⁷ The drug, marketed under the trade name Xyrem, is sodium oxybate, a sodium salt of gamma-hydroxybutyrate (GHB),¹⁸ and does not result in tolerance¹⁹ or result in adverse effects upon sudden cessation of treatment.²⁰

Because GHB's history as an abused drug is well-documented, a short summary of that history will suffice for this paper.²¹ GHB was first "marketed as an unregulated dietary supplement in health food stores, training gyms, and fitness centers, and on the Internet during the 1980s...taken to enhance body building and strength training...as a natural treatment for insomnia, and to induce weight loss."²² Although banned by FDA in 1990, by that time "GHB had developed notoriety as a substance of abuse" at dance clubs and parties, supposedly producing feelings of "disinhibition, sexual arousal, and euphoria."²³ GHB "was also

<http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3754t1.txt>).

¹³*Id.*

¹⁴Bob Cloud, Testimony before the Food and Drug Administration Peripheral and Central Nervous System Drugs Advisory Committee (June 6, 2001) (transcript available at <http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3754t1.txt>).

¹⁵Fuller and Hornfeldt, *supra* note 3, at 1206.

¹⁶*Id.*

¹⁷*Overview for Healthcare Professionals*, at <http://xyrem.info/overviewhp.htm>.

¹⁸*Id.*

¹⁹Telephone Interview with Bob Cloud, Fmr. Director, Narcolepsy Network (Mar. 4, 2004). [hereinafter Bob Cloud Interview]

²⁰U. S. Xyrem Multi-Center Study Group, *The Abrupt Cessation of Therapeutically Administered Sodium Oxybate GHB Does Not Cause Withdrawal Symptoms*, 41(2) JOURNAL OF TOXICOLOGY: CLINICAL TOXICOLOGY, 131 (2003).

²¹For a fuller discussion of the history of GHB, see Fuller and Hornfeldt, *supra* note 3.; and OFFICE OF NAT'L DRUG CONTROL POLICY, *Drug Policy Information Clearinghouse Fact Sheet: Gamma-Hydroxybutyrate (GHB)* (November 2002).

²²Fuller and Hornfeldt, *supra* note 3, at 1206.

²³*Id.* at 1207

implicated in an increasing number of drug-facilitated sexual assaults” due to its ability to cause “anterograde amnesia, especially when combined with ethanol, leaving the assault victim unable to recall details of the event.”²⁴ This led to GHB’s label as a “date-rape” drug.²⁵ At the same time, “an increasing number of people taking GHB experienced overdose requiring hospital emergency care.”²⁶ “Abuse of GHB can cause serious medical problems, including trouble breathing, seizures (convulsions), loss of consciousness, coma, and death,” and “could also lead to dependence, craving... and severe withdrawal symptoms.”²⁷ Concerns about rising GHB abuse led the Food and Drug Administration (“FDA”) to ban its use in 1990,²⁸ and Congress to list it as a schedule I drug in 2000.²⁹

This is the story of GHB’s path to legitimacy – how it came to be approved as a treatment for cataplexy associated with narcolepsy distributed under what are arguably the tightest controls of any prescription drug on the market.

The Orphan Drug Act and FDA Approval

The story of GHB’s path to legitimacy begins in January 1983, when President Ronald Reagan signed the Orphan Drug Act (PL 97-414) into law.³⁰ The Act was designed to encourage the development of what were

²⁴*Id.*

²⁵*Id.*

²⁶*Id.*

²⁷Center for Drug Evaluation and Research, *Xyrem (sodium oxybate) Oral Solution Medication Guide* (July 17, 2002) available at <http://www.fda.gov/cder/drug/infopage/xyrem/medicationguide.htm>.

²⁸Center for Drug Evaluation and Research, *BD, GBL, and GHB Poster* (May 6, 2003) available at <http://www.fda.gov/cder/news/ghb-poster.htm>.

²⁹Hillory J. Farias and Samantha Reid Date-Rape Drug Prohibition Act of 2000. Pub. L. No. 106-172. This Act provided for the bifurcated scheduling of GHB and a GHB drug product approved by FDA. This is discussed in detail in the section on legislation, below.

³⁰Maeder, Thomas, *The Orphan Drug Backlash*, SCIENTIFIC AMERICAN, May 2003, at 80, 83. This article also gives an interesting critique of the orphan drug designation and points to those drugs which were developed under the Orphan Drug Act incentives but then turn out to have much more widespread applications than initially thought. If Xyrem turns out to be effective in treating fibromyalgia and other conditions for which it is currently being studied (see discussion at the end of this paper), Orphan Medical and Xyrem may be subject to criticisms similar to those discussed by Maeder.

termed “orphan drugs.”³¹ Originally defined as a drug which could not reasonably be expected to recover development costs through US sales, a 1984 amendment allowed a presumption that such designation applied to any drug anticipated to treat fewer than 200,000 patients.³² The Act, as amended, gives several incentives to companies in order to promote development of orphan drugs, including a 50 percent tax credit on all clinical trial costs, exemption from paying the “user fee” (currently \$533,400) that the FDA usually charges drug sponsors, and bars other firms from obtaining FDA approval for the same drug for seven years.³³ Indeed, “FDA can approve the same drug made by a prospective competitor only if it is ‘clinically superior’ - if the product is safer, more effective or easier to take.”³⁴ An added, unofficial benefit for orphan drug sponsors is a closer working relationship with FDA, to the point where FDA will often assist in the design of the statistically meaningful clinical trials which are more difficult for rare disorders.³⁵ The program has been remarkably effective at encouraging development of orphan drugs, with one 2003 report stating that “229 orphan drugs that together treat 11 million patients, most with serious or life-threatening diseases, are now on the market.”³⁶

At the Congressional hearings on the Orphan Drug Act, GHB as a possible treatment for symptoms of narcolepsy was held up as a prime example of a drug no company was willing to investigate without the incentives provided by the Orphan Drug Act.³⁷ FDA began publishing a “cumulative list of orphan drug designations” in 1985 in order to give notice of those drugs which are “designated orphan drugs and biological products,”³⁸ and GHB first appeared on that list in 1986 (after being designated as an orphan drug in 1985) as a possible treatment for “narcolepsy and the auxiliary symptoms of cataplexy, sleep paralysis, hyp-

³¹Pub. L. No. 97-414, §1.

³²See Maeder *supra* note 30, at 83.

³³*Id.*

³⁴*Id.*

³⁵*Id.*

³⁶*Id.* at 82.

³⁷Bob Cloud Interview, *supra* note 19.

³⁸See, e.g. 51 FR 3844-02 and 52 FR 3778-01.

nagogic hallucinations, and automatic behavior.”³⁹ GHB was already being studied in Canada as a possible treatment for narcolepsy indications,⁴⁰ and in the United States, Dr. Martin Scharf, currently Executive Director of the Tri-State Sleep Disorder Clinic in Cincinnati, OH, had filed for and received a treatment Investigational New Drug Application (“Treatment IND”) in 1983.⁴¹ In 1985 Dr. Scharf published a report on the open label trial he was conducting which established the safety and efficacy of GHB as a treatment for narcolepsy indications,⁴² though as Dr. Scharf concedes, because his was an open label trial – meaning no placebos were used – the report was of limited utility in the development of the drug.⁴³ Subsequently, because of the high cost associated with a treatment IND for which he was not charging patients for access to the drugs, Dr. Scharf began cooperating with Biocraft, a generic drug company which had registered its intent to research GHB as an orphan drug product with the FDA.⁴⁴ However, after Biocraft was acquired by Teva Pharmaceutical Industries, it became focused on generic drug manufacturing and less interested in drug development, and thus abandoned its investigation of GHB.⁴⁵

Orphan Medical, Inc. (“Orphan”) was approached by FDA Office of Orphan Products in 1994 to begin investigation into the possible use of GHB as a treatment for narcolepsy.⁴⁶ Orphan “acquires, develops,

³⁹51 FR 3844-02 (Table).

⁴⁰See, e.g. Mamelak M, Escriu JM, Stokan O. *The effects of Gamma-hydroxybutyrate on sleep*. BIOLOGICAL PSYCHIATRY 1977;12:273-88.

⁴¹Telephone Interview with Dr. Martin Scharf, Executive Director, Tri-State Sleep Disorder Clinic (April 7, 2004) [hereinafter Martin Scharf Interview]; There are three types of INDs: 1) An Investigator IND, submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population; 2) Emergency Use IND, which allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with 21CFR , Sec. 312.23 or Sec. 312.34. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist; and 3) Treatment INDs, submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place, and which are used to make promising new drugs available to desperately ill patients as early in the drug development process as possible.

– Center for Drug Evaluation and Research, *Investigational New Drug (IND) Application Process* (Jan. 20, 2004) at <http://www.fda.gov/cder/regulatory/applications/ind.page.1.htm>; Food and Drug Administration, *Treatment IND*, available at <http://www.fda.gov/cder/handbook/treatind.htm>.

⁴²Scharf, M., Brown, D., Woods, M., Brown, L., and Hirschowitz J. *The effects and effectiveness of gamma-hydroxybutyrate in patients with narcolepsy*, JOURNAL OF CLINICAL PSYCHIATRY (1985) 46:222-225.

⁴³Martin Scharf Interview, *supra* note 41.

⁴⁴*Id.*

⁴⁵Bob Cloud Interview, *supra* note 19.

⁴⁶Telephone Interview with Dayton Reardon, Vice-President of Regulatory Affairs, Orphan Medical, Inc. (Mar. 17, 2004) [hereinafter Dayton Reardon Interview].

and markets products of high medical value that address inadequately treated or uncommon diseases within selected market segments;" according to the company, "a drug has high medical value if it offers a major improvement on the safety or efficacy of patient treatment and has no substantially equivalent substitute."

⁴⁷ In essence, it is a drug company devoted to the development of orphan drugs, and currently has seven drugs on the market with NDAs approved by FDA.⁴⁸ The FDA chose Orphan almost "by default" after the other companies decided not to move forward with development of a GHB drug product because of economic considerations;⁴⁹ at the same time, Dr. Scharf offered Orphan all of his data for free if they would agree to develop the drug product.⁵⁰ Based in part on that data, as well as on the prior designation of GHB as an orphan drug, Orphan's petition for designation of GHB as an orphan drug, filed in 1994, was approved within two weeks.⁵¹ In 1996, two years after being approached by FDA, Orphan filed and received an IND and began formal development efforts of GHB as a drug product.⁵²

According to a company representative, "the Orphan Drug Act was an incentive in the development of Xyrem. The compound was in the public domain and without the protection of the Act, it would have been less likely to be developed."⁵³ Moreover, a measure of the special relationship accorded to drug companies working under the Orphan Drug Act by FDA can be seen in Orphan's experience. The company "worked closely with FDA for several years on this medication. . . the Office of Orphan Products in particular was very supportive and interested in seeing a company move forward on this project."⁵⁴ One clear – and necessary⁵⁵ – benefit of

⁴⁷Orphan Medical, Inc., *About Orphan Medical*, available at <http://www.orphan.com/index.cfm?aid=10>.

⁴⁸Bob Cloud Interview, *supra* note 19.

⁴⁹Telephone Interview with Dr. John McCormick, Deputy Director, Food and Drug Administration Office of Orphan Products Development (April 19, 2004) [hereinafter John McCormick Interview].

⁵⁰Martin Scharf Interview, *supra* note 41.

⁵¹According to Dr. Reardon, this was the quickest designation of any drug as an orphan drug product in the program's history. Of course, as Dr. Reardon notes, the substance had already been designated as such when Biocraft was researching it, and the FDA Office of Orphan Products was quite familiar with the research.

Dayton Reardon Interview, *supra* note 46.

⁵²*Id.*

⁵³E-mail from David Folken, Senior Corporate Communications Specialist, Orphan Medical, Inc., to Ariel Neuman, Student, Harvard Law School (Mar. 16, 2004, 09:33:42 CST) (on file with author) [hereinafter David Folken Email].

⁵⁴*Id.*

⁵⁵Because, by definition, an orphan drug is meant to treat only a small population of patients, it is impossible to test the drugs on the same number of patients normally required by FDA for drug approval.

designation as an orphan drug in Orphan's case was that FDA did not require the company to study the drug in nearly as many patients as is typical in drug development research.⁵⁶

In December 1998, Orphan was granted a Treatment IND for the study of GHB in treating patients with narcolepsy and cataplexy.⁵⁷ Treatment INDs allow the study of potentially useful compounds which do not yet have enough clinical data to justify an NDA; it is "a mechanism to permit use of an investigational drug outside the context of a controlled trial for a serious disease for which there aren't other available treatments. . . usually granted relatively late in the development of a drug so that. . . (there is) some reasonable idea, based on controlled data, that the drug is probably effective and reasonably well tolerated."⁵⁸ In this case the FDA determined that a single controlled study "supported an effect of GHB" in treating narcolepsy and cataplexy patients, and Orphan committed to providing a second study as well.⁵⁹ The Treatment IND was meant to expand patient access to Xyrem while generating data necessary to support the filing of NDA for the drug.⁶⁰ Although Orphan tried to charge patients receiving GHB under the treatment IND, recovery efforts from patients and insurance companies were "pretty dismal" and did not even cover the costs of the treatment IND program.⁶¹

The IND had the desired effect - by the time Orphan submitted its NDA⁶² for Xyrem on September 30,

⁵⁶Dayton Reardon Interview, *supra* note 46.

⁵⁷Memorandum from Russell Katz, Director of FDA Division of Neuropharmacological Drug Products, to Members of FDA Peripheral and Central Nervous Systems Drug Advisory Committee (May 9, 2001) *available at* http://www.fda.gov/ohrms/dockets/ac/01/briefing/3754b1_02_section%201.pdf [hereinafter Memorandum]; Food and Drug Administration, *Product Index of Treatment INDs Allowed to Proceed* (Sept. 24, 1999) *available at* <http://www.fda.gov/oashi/patrep/treatind.html#Xyrem>.

⁵⁸Russell Katz, Testimony before the Food and Drug Administration Peripheral and Central Nervous System Drugs Advisory Committee (June 6, 2001) (transcript available at <http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3754t1.txt>) [hereinafter Katz Testimony].

⁵⁹Memorandum, *supra* note 57.

⁶⁰Press Release, Orphan Medical, Inc., Orphan Medical Initiates XyremTM (sodium oxybate) oral solution Treatment IND (Feb. 23, 1999) *available at* <http://www.orphan.com/articleDetail.cfm?aid=4&id=175>.

⁶¹Dayton Reardon Interview, *supra* note 46.

⁶²Food and Drug Administration NDA 21-196

2000, the application included results from four randomized controlled trials, as well as safety data.⁶³ The NDA requested approval of Xyrem for the treatment of both cataplexy and excessive daytime sleepiness.⁶⁴ FDA granted the application priority review status,⁶⁵ a designation which “recognizes the importance of prompt action to evaluate applications for new drugs which have the potential for important or modest therapeutic advances”⁶⁶ and which moves the application to the top of FDA’s pile. Reflecting the priority accorded to Xyrem, FDA scheduled a meeting of the Peripheral and Central Nervous System Drugs Advisory Committee (the “Advisory Committee”) for March 15, 2001, to consider the safety and efficacy of Xyrem.⁶⁷ In the months leading up to that meeting, however, a number of issues arose. Dr. Deborah Liederman, the newly appointed Director of Controlled Substances Staff at FDA, brought a new emphasis to the discussion with a focus on evaluation of safety concerns.⁶⁸ She and other officials at FDA began insisting that the drug come in a formulation with a colorant or flavorant, meant to warn potential victims of date-rape if Xyrem were slipped into their drink.⁶⁹ Orphan had previously investigated adding a colorant or flavorant but found it chemically infeasible, and eventually the chemists and others at FDA agreed.⁷⁰ In addition, because Xyrem is meant to be taken in two doses – one before going to bed and another a few hours after falling asleep⁷¹ – and because the second dose must be poured before taking the first so that the patient will not have to get out of bed, concerns arose that the poured second dose would be vulnerable to accidental ingestion by children.⁷² As a result, Orphan redesigned the packaging of Xyrem to include two child-proof

⁶³Memorandum, *supra* note 57.

⁶⁴Press Release, Orphan Medical, Inc., Xyrem® NDA for Narcolepsy Symptoms Submitted by Orphan Medical (Oct. 2, 2000) *available at* <http://www.orphan.com/articledetail.cfm?aid=4&id=203>.

⁶⁵*Id.*; Press Release, Orphan Medical, Inc., Orphan Medical Receives 90 Day Extension To Xyrem® New Drug Application (NDA), (March 30, 2001) *available at* <http://www.orphan.com/articledetail.cfm?aid=4&id=272>.

⁶⁶Food and Drug Administration, *Staff Manual Guide BD4820.3*, in PETER BARTON HUTT & RICHARD MERRILL, FOOD AND DRUG LAW: CASES AND MATERIALS 529, 531 (2nd ed. 1991).

⁶⁷66 Fed. Reg. 10305

⁶⁸Telephone Interview with Dr. Marlene Haffner, Director, Food and Drug Administration Office of Orphan Products Development (April 19, 2004) [hereinafter Marlene Haffner Interview]; Dayton Reardon Interview, *supra* note 46.

⁶⁹*Id.*

⁷⁰*Id.*

⁷¹Center for Drug Evaluation and Research, *supra* note 27.

⁷²Dayton Reardon Interview, *supra* note 46.

dosing cups, which continue to be included with the product today.⁷³

Nonetheless, the Advisory Committee meeting was ultimately postponed when FDA's Division of Scientific Investigations issued findings which "raised serious questions about the reliability of data" submitted by Orphan in support of the NDA.⁷⁴ The data in question was not from those trials conducted by or sponsored by Orphan,⁷⁵ but instead was from the trials of Dr. Scharf, the "individual investigator who had treated about 140 patients under his own IND, and whose data (representing about 1000 patient-years of exposure, or about 70% of the total patient exposure in the NDA) had been submitted by (Orphan) in support of the safety of GHB."⁷⁶ In particular, the investigators were unable to locate "critical source documents of Dr. Scharf's IND."⁷⁷ This source data consisted in large part of information on adverse events with 80 patients who were no longer under Dr. Scharf's care and whose current locations were largely unknown.⁷⁸ This problem arose in large part because Dr. Scharf's data covered 16-17 years of data for 120 patients around the country, under an open label study in which he had not kept formal case-report forms; Dr. Scharf points out that in essence FDA was holding his data which dated back to 1983 to a 2001 standard.⁷⁹ FDA contended, however, that no matter when the data was produced, one had to measure safety and efficacy by the most up-to-date standards.⁸⁰ Thus, because Dr. Scharf's data comprised almost 30 percent of the patient safety database in the NDA,⁸¹ Orphan was forced to undertake "a detailed and extensive review of Dr. Scharf's records, in an attempt to validate the presentation of this data...(and file) an amendment which contained a re-analysis of the data from Dr. Scharf's study."⁸² Dr. Scharf also made "extensive efforts" to provide the

⁷³*Id.*

⁷⁴Memorandum, *supra* note 57.

⁷⁵Press Release, Orphan Medical, Inc., Orphan Medical Reports on Xyrem NDA Developments (Mar. 1, 2001) *available at* <http://www.orphan.com/articledetail.cfm?aid=4&id=269>.

⁷⁶Memorandum, *supra* note 57.

⁷⁷Katz Testimony, *supra* note 58.

⁷⁸Dayton Reardon Interview, *supra* note 46. The safety information from the patients still under Dr. Scharf's care was available and apparently satisfactory for FDA.

⁷⁹Martin Scharf Interview, *supra* note 41.

⁸⁰Marlene Haffner Interview, *supra* note 68.

⁸¹Katz Testimony, *supra* note 58.

⁸²Memorandum, *supra* note 57.

additional source documents, and once FDA investigators reexamined the data with the missing material now included, they concluded that “the records, for the most part, do support the sponsor’s descriptions of Dr. Scharf’s data” – that GHB was relatively safe for use as a treatment of cataplexy.⁸³ Nonetheless, the delay and required submission of an amendment to the original NDA resulted in an extension of the original due date for the application, and the rescheduling of the Advisory Committee meeting to June 6, 2001.⁸⁴

At that meeting, the Advisory Committee examined both the clinical studies and the proposed risk management program.⁸⁵ It considered testimony from Orphan, FDA, outside experts on both GHB and risk management, patients, patient advocates, drug diversion specialists, and opponents of any GHB drug product.⁸⁶ FDA originally asked the Advisory Committee to vote on three questions: 1) whether or not substantial evidence of effectiveness had been submitted for the indication for cataplexy and excessive daytime sleepiness in patients with narcolepsy; 2) whether or not GHB can be considered safe in use given appropriate labeling if the Advisory Committee found that there is substantial evidence of effectiveness for only a particular indication; and 3) whether or not it is required or should be required that the drug be approved only with the risk management program of some type (not necessarily the one specifically proposed by the company).⁸⁷ Nonetheless, the Advisory Committee actually took a number of votes, the results of which are laid out in the table below.⁸⁸

<u>Question</u>	<u>Yes</u>	<u>No</u>	<u>Abstentions</u>
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⁸³Katz Testimony, *supra* note 58.

⁸⁴Memorandum, *supra* note 57.

⁸⁵Food and Drug Administration Peripheral and Central Nervous System Drugs Advisory Committee Meeting Transcript (June 6, 2001) (available at <http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3754t1.txt>) [hereinafter Transcript].

⁸⁶*Id.* The slides from the presentations made to the FDA Advisory Committee are available at <http://www.fda.gov/ohrms/dockets/ac/01/slides/3754s1.htm>.

⁸⁷Katz Testimony, *supra* note 58.

⁸⁸Note: only those questions where votes were counted and reported are included. Except where noted, all information in this table is taken from Final Minutes of the Food and Drug Administration Peripheral and Central Nervous System Drug Advisory Committee of June 6, 2001 (available at <http://www.fda.gov/ohrms/dockets/ac/01/minutes/3754m1.htm>).

Has the sponsor demonstrated efficacy (at 9 grams) of Xyrem for the proposed indication of cataplexy? ⁸⁹	6	3	—	
Has the sponsor demonstrated efficacy (at 6 – 9 grams) of Xyrem for the proposed indication of cataplexy?	5	4	—	

⁸⁹This vote is not included in the Advisory Committee’s Final Minutes. It is indicated, however, in the Transcript, *supra* Note 85, and is reported at Press Release, Orphan Medical Inc., Orphan Medical, Inc. Announces FDA Advisory Committee Finds Xyrem® Effective For Treating Cataplexy Associated With Narcolepsy (June 6, 2001) *available at* <http://www.orphan.com/articledetail.cfm?aid=4&id=286>.

Has the sponsor demonstrated efficacy (at 6 – 9 grams) of Xyrem for the proposed indication of day-time sleepiness?	0	9	—	
Has the sponsor established the safety of Xyrem when used for the proposed indication for which substantial evidence of effectiveness has been submitted? ⁹⁰	4	4	1	

⁹⁰This was only voted on in terms of cataplexy and with a dose range of 6-9grams/day.

Is the adoption of a risk management plan necessary for the safe use of Xyrem?	8	1	—	
Should there be a requirement for additional safeguards in patient's homes, e.g., keeping drugs in a locked storage space?	1	8	—	
Should patients sign an informed consent form before receiving the initial shipment of the drug?	5	4	—	
Should physicians document that they read the materials sent to them before the pharmacy fills the initial prescription?	7	2	—	
Should physicians be required to demonstrate safe use and appropriate dosage preparation to patients before the first prescription and be required to document that it has been accomplished? ⁹¹	1	7	1	
Should there be restricted prescribing for the product? (e.g., only to those who have a diagnosis of cataplexy)	7	1	1	
Should certification of physicians for prescribing Xyrem be required?	0	8	1	

Thus, the Advisory Committee recommended that Xyrem be approved only for the treatment of cataplexy,

⁹¹The word physician staff was added to the sentence.

and that it must be accompanied by a comprehensive risk management program.

On July 2, 2001, FDA determined that Xyrem was approvable for the indication of cataplexy related to narcolepsy.⁹² However, it would be a full year before Xyrem was approved for sale.⁹³ FDA first sent an Approvable Letter to Orphan stating that, before final approval of the Xyrem NDA, FDA required a safety update of on-going clinical trials, an additional acute exposure trial in respiratory compromised patients, definition of final product labeling, minor modifications to the proposed risk management program, and that Orphan undergo a successful good manufacturing practices (GMP) re-inspection and a pre-approval inspection relating to manufacture of Xyrem.⁹⁴ Although Orphan tried to respond to FDA's concerns with its NDA Amendment of October 9, 2001,⁹⁵ FDA sent another approvable letter in April 2002, requiring further clarification of respiratory data and revisions to labeling.⁹⁶ In addition, FDA indicated that it would conduct additional clinical trial site review, which it eventually completed but about which it issued no findings.⁹⁷ Orphan responded again on May 17,⁹⁸ and FDA accepted the response and set July 17, 2002, as the action goal for the approval of Xyrem.⁹⁹ During this year-long process, according to Dayton Reardon, Orphan's vice-president for regulatory affairs, the "NDA was put under extraordinary scrutiny... there was not a single piece of paper that was left unturned" and FDA examined every case report for every patient.¹⁰⁰

⁹²Press Release, Orphan Medical, Inc., Orphan Medical, Inc. Receives FDA Approvable Letter for Xyrem® (July 3, 2001) *available at* <http://www.orphan.com/articledetail.cfm?aid=4&id=288>.

⁹³*Xyrem Clinical Development*, Biospace, *at* <http://www.biospace.com/ccis/detail.cfm?ClinicalID=715>.

⁹⁴Orphan, at the time of the Approvable Letter, was subject to a warning letter from the FDA with respect to GMP not related to Xyrem, which was the reason for the GMP requirements. Press Release *supra* note 92.

⁹⁵Press Release, Orphan Medical, Inc., Orphan Medical, Inc. Submits Complete Response To The Xyrem® (Sodium Oxybate) NDA Approvable Letter, (Oct. 9, 2001) *available at* <http://www.orphan.com/articledetail.cfm?aid=4&id=294>.

⁹⁶Press Release, Orphan Medical, Inc., Orphan Medical, Inc. Submits A Complete Response To The Xyrem® (Sodium Oxybate) NDA Approvable Letter (May 17, 2002) *available at* <http://www.orphan.com/articledetail.cfm?aid=4&id=320>.

⁹⁷*Id.*

⁹⁸In that response Orphan made the requested changing to its labeling, changes which it did not think were necessary and with which it still does not agree. – Dayton Reardon Interview, *supra* note 46.

⁹⁹Press Release, Orphan Medical, Inc., Orphan Medical, Inc. Release: Xyrem® Response Accepted By FDA For Review (May 23, 2002) *available at* <http://www.orphan.com/articledetail.cfm?aid=4&id=323>.

¹⁰⁰Dayton Reardon Interview, *supra* note 46.

On July 17, 2002, FDA announced its approval of Xyrem for treating “patients with narcolepsy who experience episodes of cataplexy.”¹⁰¹ The FDA did so while adopting all of the Advisory Committee’s recommendations except a restriction on off-label prescribing; this violated FDA’s long-standing policy of declining to interfere with “the practice of medicine.”¹⁰² The approval was made under 21 CFR 314 Subpart H, which provides for the accelerated approval of new drugs for serious or life-threatening illnesses.¹⁰³ Subpart H, passed in 1992, was originally a response to the AIDS epidemic,¹⁰⁴ but has since been used to approve at least 49 NDAs for various indications.¹⁰⁵ The Subpart allows for “marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit;” in essence meaning the drug can be approved with less clinical data than normal, though with the requirement of further study of efficacy and safety.¹⁰⁶ A less frequently used application of Subpart H also allows FDA to place restrictions on the distribution and marketing of the approved drug in order to assure “safe use” and to expedite withdrawal of approval upon specific findings.¹⁰⁷ Xyrem was approved both based on a surrogate endpoint and with restrictions on distribution and marketing.¹⁰⁸

¹⁰¹Food and Drug Administration, *FDA Talk Paper: FDA Approves Xyrem for Cataplexy Attacks in Patients with Narcolepsy*, (July 17, 2002) at <http://www.fda.gov/bbs/topics/answers/2002/ans01157.html>

¹⁰²Not only did this recommendation violate FDA policy, but it was most likely not a legally defensible position for FDA to take, according to the agency’s general counsel office. John McCormick Interview, *supra* note 49.

¹⁰³Letter from Dr. Robert Temple, Director of Office of Drug Evaluation I, Center for Drug Evaluation and Research, to Dayton Reardon, Vice-President of Regulatory Affairs, Orphan Medical, Inc. (July 17, 2002) [hereinafter Temple Letter].

¹⁰⁴Susan B. Anthony List, *Cutting Corners, Risking Lives: How the Clinton FDA Endangered Women by Rushing Approval of RU-486*, at <http://www.sba-list.org/RU-486.htm>.

¹⁰⁵Food and Drug Administration, Center for Drug Evaluation and Research, *NDAs Approved Under Subpart H*, (Sept. 30, 2003) at <http://www.fda.gov/cder/rdmt/accapp.htm>.

¹⁰⁶21 CFR 314.510

¹⁰⁷21 CFR 314.500-560

¹⁰⁸Dayton Reardon Interview, *supra* note 46.

Orphan initially resisted efforts to have the drug approved under Subpart H; it believed that the risk management program it had voluntarily devised was sufficient, it did not like the possibility of expedited withdrawal, and it feared the restrictions on marketing that came with approval under Subpart H.¹⁰⁹ Those restrictions included a requirement that all promotional materials be submitted to FDA 30 days prior to use,¹¹⁰ and thus does not allow a company to “push the boundaries” of allowable advertising that normal, *ex post* FDA-review permits.¹¹¹ FDA in this instance also required the adoption of the risk management program which Orphan had devised, distribution to patients of a “medication guide” along with the drug, at least three specified post-marketing clinical studies, submission of the final printed label which had previously been agreed upon by FDA and Orphan, and updates to FDA every three months.¹¹² While unusual – only five other NDAs approved under Subpart H have had restrictions on distribution¹¹³ – these restrictions, explained in detail below, reflected the desire to get the drug to patients as quickly as possible while ensuring safe distribution and use of Xyrem. The approval under Subpart H represented an agreement between the Orphan and FDA that the risk management program would be instituted.¹¹⁴

Congress Takes Action

In the midst of this development process, FDA and Orphan faced an unexpected challenge – from Congress. Following the 1990 FDA ban on the sale of GHB, momentum began to build for Congressional action. A spike

¹⁰⁹*Id.*

¹¹⁰Promotional materials to be used within the first 120 days must be submitted to FDA prior to approval. Promotional material used after the 120 day period need only be submitted 30 days in advance of use. 21 CFR 315.550

¹¹¹Dayton Reardon Interview, *supra* note 46.

¹¹²Temple Letter, *supra* note 103. The details of FDA’s requirements for distribution of Xyrem are available at <http://www.fda.gov/cder/foi/label/2002/21196lbl.pdf>. The risk management program, as adopted, is also described in detail later in this paper.

¹¹³Food and Drug Administration, Center for Drug Evaluation and Research, *NDAs Approved Under Subpart H*, (Sept. 30, 2003) at <http://www.fda.gov/cder/rdmt/accapp.htm>.

¹¹⁴John McCormick Interview, *supra* note 49.

in reported deaths from GHB overdoses, as well as an increased number of both violent and non-violent date-rapes involving GHB, prompted members of Congress to begin seeking to list GHB as a Schedule I controlled substance.¹¹⁵ According to one sponsor of the final Congressional legislation speaking in 2000, “The abuse, trafficking, and diversion of GHB is rapidly increasing. The Drug Enforcement Administration (“DEA”) has documented nearly 6,000 encounters of GHB. Deaths from the drug are escalating rapidly, from one in 1990 to 17 last year, for a total of 58 deaths. Emergency room episodes resulting from the use of the drug are also escalating rapidly, from 20 in 1992 to 762 in 1997, the last year for which data is available, for a total of more than 1,600 episodes;” Congressional action was finally “sparked by the death of two young, wonderful women, one in Texas and one in Michigan, whose drinks were spiked with GHB. Since then, five more women have died in Texas and another two in Michigan.”¹¹⁶ The DEA was also pushing for the scheduling of GHB as a Schedule I substance,¹¹⁷ pointing out in testimony before Congress that between 1993 and 1999 “more than 3,500 GHB-related cases of abuse, overdose, possession, illegal manufacturing, illicit diversion and trafficking (were) documented by Federal, state and local officials.”¹¹⁸

As public pressure increased, the first bill attempting to criminalize the production, use, and sale of GHB was introduced in 1997.¹¹⁹ This bill, introduced by Representative Sheila Jackson-Lee (D-TX), was a straightforward attempt to ban GHB – it simply added GHB to the list of Schedule I drugs under the Controlled Substances Act (21 U.S.C. 812) and directed the Attorney General to “establish programs throughout the United States and disseminate materials to provide young people in high school and college with education about the use of controlled substances in the furtherance of rape and sexual assault.”¹²⁰ The bill was referred

¹¹⁵146 Cong Rec H 55

¹¹⁶146 Cong Rec H 55 – Comments by Cong. Upton

¹¹⁷Dayton Reardon Interview, *supra* note 46.

¹¹⁸Terrance Woodworth, Deputy Director, Office of Diversion Control, Drug Enforcement Administration, Testimony Before the: House Commerce Committee Subcommittee on Oversight and Investigations (March 11, 1999) (available at <http://www.usdoj.gov/dea/pubs/cngrtest/ct990311.htm>).

¹¹⁹105 H.R. 1530 (“The Hillary J. Farias Date Rape Prevention Drug Act”)

¹²⁰*Id.* at §3

to the House Commerce Committee and House Judiciary Committee, but no further action was taken during the 105th Congress.¹²¹ Representative Jackson-Lee reintroduced her legislation during the 106th Congress as 106 H.R. 75, but by this point it appears that momentum had shifted from an outright ban on GHB to the bifurcated scheduling that eventually became law. While the original Jackson-Lee bill had thirteen co-sponsors, the re-introduced bill had none.¹²²

Instead, after lobbying by Orphan and various narcolepsy patient interest groups,¹²³ the Congressional sponsors decided that they should attempt “to fashion a remedy (to GHB abuse) without limiting its potential for medical use for the benefit of society.”¹²⁴ Patient groups, such as the Narcolepsy Network, viewed the pure Schedule I listing of GHB as “extremely unfortunate,” and worked with Orphan to convince legislators that a door must be left open for the possible use of GHB as a treatment for cataplexy.¹²⁵ Orphan in fact believed that GHB should be either a Schedule IV or unscheduled substance, but found this position to be untenable in the face of DEA opposition.¹²⁶

Orphan took the lead on pushing for some sort of compromise solution.¹²⁷ It took a lesson from what it believed were the mistakes made by Hoffman-LaRouche, the manufacturer of Rohypnol (flunitrazepam), during negotiations regarding The Drug-Induced Rape Prevention and Punishment Act of 1996 (Pub. L.104-305).¹²⁸ According to Orphan’s consultants, Hoffman-LaRouche had initially held discussions and negotiations with law-enforcement and rape-crisis advocates, as well as other stakeholders, about a compromise scheduling for flunitrazepam, only to do an “end-run” around them on the floor of the house and have the compound remain

¹²¹143 Cong Rec H 2168

¹²²105 H.R. 1530; 106 H.R. 75

¹²³FDA was not involved in any lobbying efforts because it is prohibited by law from lobbying Congress. – Marlene Haffner Interview, *supra* note 68.

¹²⁴Telephone Interview with Bart Stupak, United States Representative, Michigan District 1 (Feb. 24, 2004) [hereinafter Bart Stupak Interview].

¹²⁵Bob Cloud Interview, *supra* note 19.

¹²⁶Dayton Reardon Interview, *supra* note 46. According to Dr. Reardon, the DEA insisted on a Schedule I designation.

¹²⁷David Folken Email, *supra* note 53; Telephone interview with Bob Gagne, Strategic and Crisis Consultant, Colle + McVoy Public Affairs (April 8, 2004) [hereinafter Bob Gagne Interview].

¹²⁸*Id.*

a Schedule IV substance but with Schedule I penalties for illicit use and distribution.¹²⁹ This left the stakeholders with a deep distrust of drug companies and made Orphan's job even more difficult.¹³⁰ Thus Orphan adopted a strategy whereby it became an ally of the stakeholders, pushing for the controls that they wanted while at the same time educating them about the potential benefits of pharmaceutical GHB.¹³¹ Beginning in 1999, Orphan representatives met with prosecutors, rape-crisis advocates, law-enforcement representatives, and other stakeholders in order to learn their concerns and desires and in an attempt to establish a rapport of mutual good will.¹³² At the meetings, Orphan attempted to built bridges of trust between the company and those who were concerned about abuse and illicit use of GHB, thereby allowing the stakeholders to support Orphan's efforts because Orphan was supporting theirs.¹³³ These conversations eventually led to both Orphan and the stakeholders pushing for provisions that made it into the final bill, such as the listing of GBL, a GHB analogue, as a controlled substance, the development of GHB field-test kits for use by law enforcement, and better, coordinated investigation techniques for drug-related date rapes.¹³⁴ Thus Orphan was able to count these stakeholders as allies as it began its direct lobbying of Congress; its strategy boiled down to pushing for greater controls of GHB's illicit use, with an almost incidental inclusion of an exception for the development of an FDA-approved drug product.¹³⁵

At the same time, Orphan helped organize and fund correspondence, testimony, and meetings between narcoleptics who might benefit from prescription GHB and the various state and federal legislators working on the issue.¹³⁶ Orphan was concerned that "as a responsible public company, it would need to halt its

¹²⁹*Id.*; Pub. L. 104-305

¹³⁰Bob Gagne Interview, *supra* note 127.

¹³¹*Id.*

¹³²*Id.*

¹³³*Id.*

¹³⁴*Id.*; Pub. L. 106-172

¹³⁵Bob Gagne Interview, *supra* note 127.

¹³⁶Bob Cloud Interview, *supra* note 19.

research if (GHB) were placed (only) in schedule I.”¹³⁷ The company did its own direct lobbying, educating the sponsors of the Congressional legislation on the debilitating effects of cataplexy and narcolepsy, as well as the potential benefits to the patients of prescription GHB.¹³⁸ It argued that “the problem of GHB abuse was due to criminals making the compound illegally, and by making GHB a schedule I substance it was unlikely that people breaking the law already would suddenly stop. . . Thus, the problem of GHB abuse would likely still be there but the hope of a legitimate medication may well disappear.”¹³⁹ Meanwhile, FDA recognized that GHB “needed to be scheduled in order to deal with the misuse of the product that was being made in bathtubs and to get precursors of the product out of the system,” while recognizing the importance of the development of a GHB drug-product.¹⁴⁰ Although it is not clear which division at FDA initially came up with the suggestion, on May 19, 1999, the Department of Health and Human Services, which houses FDA, recommended a dual scheduling of GHB, recommending that GHB be scheduled in Schedule I of the CSA and the GHB prescription drug product be scheduled in Schedule III if studied under a FDA authorized Investigational New Drug (IND) exemption.¹⁴¹ Orphan accepted this suggestion because the bifurcated scheduling was “a good win-win solution which allowed for the continued development of an important medication while still allowing for, and encouraging, strong prosecution of anyone that would misuse the compound.”¹⁴²

The death of Samantha Reid in 1999 in Michigan was a defining factor in the scheduling of GHB.¹⁴³ The use of the drug in the attempted rape of a fifteen year old galvanized the Michigan delegation to Congress.¹⁴⁴

¹³⁷David Folken Email, *supra* note 53.

¹³⁸Bart Stupak Interview, *supra* note 124.

¹³⁹David Folken Email, *supra* note 53.

¹⁴⁰John McCormick Interview, *supra* note 49.

¹⁴¹106 H.Rpt.340; Part 1; Letter from HHS to DEA, published at 65 Fed. Reg. 13236-37 (March 2000)

¹⁴²David Folken Email, *supra* note 53.

¹⁴³145 Cong Rec S 14870, 14873; 146 Cong Rec H 55, 57.

¹⁴⁴Bart Stupak Interview, *supra* note 124.

House Commerce Committee Subcommittee on Oversight and Investigations Chairman Fred Upton's (R-MI) district pushed the legislation through the House of Representatives, while Senator Edmond Spencer Abrahams took the lead in the Senate.¹⁴⁵ By this point "At least 20 States (had) scheduled GHB under State drug control statutes, and law enforcement officials continue to experience an increased presence of the drug in sexual assaults, driving under the influence (DUI) offenses, and overdose cases involving teenagers."¹⁴⁶ The Subcommittee held a hearing on March 11, 1999, and received testimony from, among others, representatives of law enforcement agencies, members of Congress, a representative from Orphan, and pharmacologists.¹⁴⁷ On June 10, the name of the victim from Representative Upton's district, Samantha Reid, was added to the legislation and it was introduced as H.R. 2130 in the 106th Congress as the "Hillory J. Farias and Samantha Reid Date-Rape Drug Prohibition Act of 2000."¹⁴⁸

Representative Upton was the sponsor with an even bipartisan split of twenty co-sponsors.¹⁴⁹ This new legislation was more complex and nuanced than the original bills introduced by Representative Jackson-Lee. The House Findings recognized that "A human pharmaceutical formulation of (GHB) is being developed as a treatment for cataplexy, a serious and debilitating disease."¹⁵⁰ As part of that finding, 106 H.R. 2130 included the first-ever bifurcated scheduling of a substance under the Controlled Substances Act (21 USC 812) ("CSA"). While §3(a) added GHB to the list of Schedule I substances, §3(b) amended the Schedule III listing to include GHB "and its salts, isomers, and salts of isomers contained in a drug product for which an application has been approved under section 505 of the Federal Food, Drug, and Cosmetic Act," thereby allowing research on medical use of GHB and eventual prescription use of the substance. In an added

¹⁴⁵106 H.R. 2130; 106 S. 1561.

¹⁴⁶106 H.Rpt. 340; Prt 1.

¹⁴⁷*Id.*

¹⁴⁸145 Cong Rec H 4127.

¹⁴⁹106 H.R. 2130.

¹⁵⁰106 H.R. 2130 §2(5).

acknowledgment of the dangers of GHB, however, the legislation in §3(e) set forth Schedule I level penalties for the “unlawful use of an approved drug product that contains GHB;”¹⁵¹ this also was an unprecedented move, prompted in large part by a desire to further control the spread of GHB and halt its abuse.¹⁵²

This legislation was only the third time in history that such a bifurcated schedule was attempted. In 1986, Marinol (and any other drugs of the same formulation approved by FDA), a drug used for treating nausea and vomiting associated with cancer chemotherapy and which is made from synthetic THC, the active ingredient in marijuana, was transferred to Schedule II by DEA while marijuana and any other formulations of THC remained Schedule I substances.¹⁵³ That bifurcated scheduling, however, was not based on Congressional action, but instead came as a result of DEA statutory interpretation and petition by FDA and others.¹⁵⁴ Unlike the Date-Rape Drug Prohibition Act, the administrative ruling regarding Marinol and the Drug-Induced Rape Prevention and Punishment Act of 1996 (the only other bifurcated scheduling of a substance) were not attempts to bifurcate the scheduling of a substance in one move. Marijuana was already scheduled as Schedule I and the administrative ruling simply moved FDA-approved drug products containing synthetic THC to Schedule II;¹⁵⁵ similarly, as previously noted, the Drug-Induced Rape Prevention and Punishment Act of 1996 provided for Schedule I penalties for illicit use of flunitrazepam while maintaining its status as a Schedule IV substance.¹⁵⁶ The Date-Rape Drug Prohibition Act, on the other hand, was intended both to schedule GHB as Schedule I and any GHB drug product as Schedule III, at the same time.¹⁵⁷

The legislation was referred to both the House Committee on the Judiciary and to the House Committee

¹⁵¹106 H.Rpt. 340; Prt 1.

¹⁵²Bart Stupak Interview, *supra* note 124.

¹⁵³61 FR 35928.

¹⁵⁴51 FR 17476-01.

¹⁵⁵51 FR 17476-01. Note: In 1999, the DEA downgraded the scheduling of Marinol and other drug products containing synthetic THC to Schedule III. 61 FR 35928.

¹⁵⁶Pub. L. 104-305.

¹⁵⁷106 H.R. 2130.

on Commerce, the latter of which took control of evaluating and approving the legislation.¹⁵⁸ On July 27, the House Subcommittee on Health and Environment approved the bill for full committee consideration, and on August 5, the Committee on Commerce ordered the legislation reported to the full House.¹⁵⁹ The report was filed on September 27, and fifteen days later the legislation was approved by the entire House of Representatives by a vote of 423 to 1.¹⁶⁰ Indeed, according to Congressman Bart Stupak (D-MI), one of the original co-sponsors of the legislation, there was no real opposition at all to the bifurcated scheduling at any point in the process,¹⁶¹ and indeed, the only Representative to vote nay was Ron Paul (R-TX) who opposed the entire bill on ideological grounds of federalism.¹⁶²

Meanwhile, an almost parallel bill was moving through the Senate. On the same day that the House Committee on Commerce reported H.R. 2130 to the full House, Senator Edmond Spencer Abraham (R-MI) introduced 106 S. 1561 for consideration, also with an even bipartisan split of cosponsors¹⁶³. The bill was referred to the Senate Judiciary committee,¹⁶⁴ and was reported to the full Senate on November 18.¹⁶⁵ S. 1561 “amended H.R. 2130 to further develop and strengthen the Department of Justice’s focus on GHB and to provide for the development of forensic field tests for the detection of this substance. In all other respects, the Senate amendments (had) the same effect as the legislation” passed in the House.¹⁶⁶ The Senate amendments had no effect on the bifurcated scheduling of GHB, and once again recognized the importance of allowing research and possible development of the substance to be used as a prescription treatment for

¹⁵⁸145 Cong Rec H 4127; 145 Cong Rec D 946; 145 Cong Rec H 9822.

¹⁵⁹106 H.Rpt. 340; Prt 1.

¹⁶⁰145 Cong Rec H 9876.

¹⁶¹Bart Stupak Interview, *supra* note 124.

¹⁶²146 Cong Rec H 55, 61.

¹⁶³106 S. 1561; Note: The original short title of the Senate bill was the “Date-Rape Drug Control Act of 1999.” This was amended on November 19, 1999, to make the title the same as that of the House legislation.

¹⁶⁴145 Cong Rec S 10390.

¹⁶⁵145 Cong Rec S14805.

¹⁶⁶146 Cong Rec H 55, 55.

cataplexy.¹⁶⁷ Once again, the legislation faced no real opposition, and only one day after being referred to the full Senate, the amended legislation was passed by unanimous consent.¹⁶⁸ On January 31, 2000, the House considered the amended version of the bill under a suspension of the rules, and passed the legislation by a vote of 339 to 2.¹⁶⁹ President Clinton signed the bill into law as Public Law 106-172 on February 18.

As the legislation moved to becoming law, the public officials involved were clearly focused on the abuses and deaths resulting from GHB, as per the strategy Orphan adopted for its lobbying efforts. At the same time, the sponsors of the legislation never lost sight of their goal of making it legal to research and possibly produce a prescription GHB drug product to treat cataplexy. When speaking on the floor of the House in support of the version of the bill as amended by the Senate, Congressman Stupak, one of the original co-sponsors, took time to especially note that though “the Senate-passed version (did) not specifically schedule GHB on the list of controlled substances, but rather instruct(ed) the DEA about how the scheduling should occur. . . Congress clearly intends that once GHB is approved by the FDA, the DEA should place the drug into Schedule III. . . Only in this way can we ensure that patients who need this drug will have access to it.”

¹⁷⁰ Indeed, an example of the balancing the legislators thought they had achieved can be gleaned from the comments by the original sponsor of the anti-GHB legislation, Representative Jackson-Lee, in support of passing the final bill:

¹⁶⁷106 S. 1561.

¹⁶⁸145 Cong Rec S 14870.

¹⁶⁹146 Cong Rec H 66.

¹⁷⁰146 Cong Rec H 55, 60. Despite the Senate amendments, there was no real doubt about how GHB should be scheduled based on the final language of Public Law 106-172, the very language used amended to the bill in the Senate. As the DEA noted in its final rule published on the scheduling of GHB, “Section (3)(a)(1) of Public Law 106-172 directs the Attorney General, notwithstanding sections 201(a), 201(b), 201(c), and 202 of the CSA (21 U.S.C. 811(a), 811(b), 811(c) and 812), to issue a final order placing GHB in the same schedule as would apply to a scheduling of a substance under section 201(h)(1) of the CSA (21 U.S.C 811(h)(1)). All substances controlled under 201(h)(1) are placed in Schedule I. . . Section (3)(a)(1)(B) of Public Law 106-172 directs that a drug product containing GHB for which an application is approved under section 505 of the FFDCA, shall be placed in the schedule recommended in the last sentence of the fourth paragraph of the DHHS May 19, 1999, letter. This sentence recommends Schedule III.” 65 Fed. Reg. 13236-37 (March 2000).

“My position does not mean I am insensitive to the concerns of patients who might be helped by this drug. This drug has shown some benefits to patients with a specific form of narcolepsy in clinical trials, those who suffer from sleeping sickness, and for those uses during trials to try to cure that disease. There is a possibility that GHB can be used for the treatment of such diseases. We want that to occur, because it is a rare disorder. We believe that this bill matches the medicinal needs along with the needs to protect our citizens from the devastation of illegal use of GHB, known to be made in bathtubs in large amounts. The distribution of this drug would be strictly controlled to ensure that only patients in need of this drug would have access.”¹⁷¹

Clearly, Orphan and the patients’ groups had accomplished what they set out to do – educate legislators about both the disease and the possibility for relief that GHB provided, and impress upon them the importance of allowing further research. As Congressman Stupak said on the floor of the House, “this bill recognizes that well-designed legislative efforts should not throw the baby out with the bathwater, so to speak...the abusive use of GHB we have been focusing on should not prevent possible legitimate or beneficial uses of the drug.”¹⁷² Even President Clinton took time in his signing statement to specifically note that the legislation “will not impede ongoing research into the potential legitimate use of this drug to treat the special needs of those suffering from narcolepsy.”¹⁷³ The door was now open for Orphan to continue its investigations of GHB’s potential as a prescription drug, and cataplexy patients around the country could retain their hope that a treatment for their condition might soon be available.¹⁷⁴

To ensure that the door would remain open, Orphan continued its lobbying efforts in the individual states, many of which do not automatically adopt federal scheduling guidelines. Using a similar strategy of becoming an advocate for stakeholders such as law-enforcement and rape-crises advocates (and thus establishing the good-will whereby it could then push for Xyrem to be listed as Schedule III), Orphan continued pushing for greater controls of illicit GHB as well as stronger rape prevention and punishment laws, while at the same

time educating state law-makers about the potential benefits of medical GHB.¹⁷⁵ As a result of Orphan's efforts, as of April 2004, 43 states have adopted the Schedule I / Schedule III bifurcated schedule, while New Hampshire and Louisiana list GHB as a Schedule II substance, South Dakota lists it as a Schedule III, and Tennessee lists it as a Schedule IV; only Hawaii and Oklahoma list GHB as a Schedule I substance, thus precluding the prescription of Xyrem in those two states.¹⁷⁶

Risk Management Program for Xyrem

The Date-Rape Drug Prohibition Act allowed the Attorney General to establish strict reporting guidelines for the distribution of a GHB drug product, separate and apart for those required for other controlled substances.¹⁷⁷ Manufacturers could be required to make quarterly reports to the Attorney General on all acquisition and distribution transactions.¹⁷⁸ Moreover, each prescribing practitioner could be required to maintain files that would "be available for inspection and copying by the Attorney General" and that included, among other things, the prescribing practitioner's Federal and State registration numbers, verification that the prescribing practitioner possesses the appropriate registration to prescribe the drug product, the patient's name and address, the name of the patient's insurance provider and documentation by a medical practitioner of the patient's medical need for the drug.¹⁷⁹ These powers were in addition to the powers already granted to the Attorney General under 21 USC §827, allowing him to require registration and re-

¹⁷⁵Bob Gagne Interview, *supra* note 127.

¹⁷⁶*Id.*

¹⁷⁷Pub. L. 106-172, §4

¹⁷⁸*Id.* amending 21 U.S.C. 827, allowing the Attorney General to require reporting of "all manufacturing transactions both inventory increases, including purchases, transfers, and returns, and reductions from inventory, including sales, transfers, theft, destruction, and seizure, and shall provide data on material manufactured, manufactured from other material, use in manufacturing other material, and use in manufacturing dosage forms."

¹⁷⁹*Id.*

porting by manufacturers of various controlled substances. GHB could thus be subject to the strictest and broadest registration and reporting requirement of almost any controlled substance. While these reporting requirements were quite onerous compared with those placed on other prescription drugs, Congress was concerned that “off-label use could be tremendous,” and wanted to ensure that prescription and distribution occurred in a very “controlled setting.”¹⁸⁰

As part of its efforts to win approval and support for Xyrem, Orphan took its risk management program to an even higher level, instituting restrictions on distribution that were unprecedented in the industry.¹⁸¹ Although neither the Date-Rape Prohibition Act nor FDA required Orphan to design a closed distribution system,¹⁸² and despite the opposition to such a system from the large National Association of Chain Drug-stores, Orphan designed the most centralized prescription drug distribution system in the country, largely on its own initiative.¹⁸³ The company “began working through the appropriate controls and responsible use of Xyrem in advance of the (Date-Rape Drug Prohibition Act). . . (Orphan) did not want the misuse of a compound to potentially erase the potential of Xyrem for the treatment of cataplexy/narcolepsy. (The company was) committed to helping these patients without adding to the problem of GHB misuse. That is why (Orphan) talked with all the essential parties involved to get input on how” best to meet those goals.”¹⁸⁴ Orphan consulted with drug diversion investigators, field law enforcement, forensics experts, toxicologists, pharmaceutical distribution experts, and drug abuse trend experts to design a system that would “ensure that patients who desperately need the medicine can get it. . . (while keeping) it out of the hands of those

¹⁸⁰Bart Stupak Interview, *supra* note 124.

¹⁸¹E-mail from John Burke, Vice-President, National Association of Drug Diversion Investigators, to Ariel Neuman, Student, Harvard Law School (Feb.18, 2004, 21:08:43 EST) (on file with author) [hereinafter John Burke Email].

¹⁸²Although both the legislation and FDA had placed restrictions on distribution, neither had explicitly required a closed distribution system – this was Orphan’s idea. Pub. L. 106-172; Marlene Haffner Interview, *supra* note 68.

¹⁸³Telephone Interview with Kathy Keough, Executive Director, National Association of State Controlled Substance Authorities (Feb. 23, 2004) [hereinafter Kathy Keough Interview]; John McCormick Interview, *supra* note 49.

¹⁸⁴David Folken Email, *supra* note 53.

people who might abuse it.”¹⁸⁵

The distribution system included one single manufacturing plant and one single pharmacy which would be responsible for distributing all Xyrem prescriptions from around the nation.¹⁸⁶ Among those consulted was the National Association of Drug Diversion Investigators (“NADDI”),¹⁸⁷ and the National Association of State Controlled Substances Authorities (“NASCSA”).¹⁸⁸ Orphan invited NADDI and NASCSA representatives, along with others, to a conference at the special pharmacy and, after a presentation on the proposed risk-management program, asked them to be critical of the program¹⁸⁹ and poke holes in the system.¹⁹⁰ Both organizations felt that Orphan was truly interested in getting input and reaching a consensus on an effective system,¹⁹¹ and according to Orphan, “the input from these groups had a large impact in how the system was built.”¹⁹² NASCSA sent a representative from its board who had both a law enforcement and regulatory background, and that representative was “blown away” by the security of the program, thinking that in some respects the controls even amounted to “overkill.”¹⁹³ The NADDI representatives were equally impressed with the “unprecedented” restrictions, and had very few, if any, suggestions for improvements to the system.¹⁹⁴ According to John Burke, vice-president of NADDI and one of the representatives sent to

¹⁸⁵Patti Engel, Testimony before the Food and Drug Administration Peripheral and Central Nervous System Drugs Advisory Committee (June 6, 2001) (transcript available at <http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3754t1.txt>) [hereinafter Patti Engel Testimony].

¹⁸⁶*Id.*

¹⁸⁷NADDI is “is a unique membership organization whose members are responsible for investigating and prosecuting pharmaceutical drug diversion. . . NADDI’s principle activities comprise: (1) cooperative education and training in the specifics of pharmaceutical drug diversion, investigation, prosecution and prevention; (2) the sharing of investigative information and communication with a wide variety of interested parties with regard to the nature, scope and impact of pharmaceutical drug diversion; and (3) the development of more effective measures to combat the problem.” – NADDI, *Overview* (2004) at <http://www.naddi.org/overview.asp>.

¹⁸⁸NASCSA’s membership is comprised mainly of state agencies with controlled substances responsibility. Controlled substances responsibility” includes “the scheduling of controlled substances; the issuance of controlled substances registrations (or approval for such issuance by another agency); enforcement of state controlled substances acts; responsibility for the administrative modification of controlled substances registrations by means of suspension, revocation, cancellation, probational or conditional issuance or continuance of registration, or the responsibility for issuance of any professional license which gives the agency authority to issue, modify, suspend, revoke, or otherwise affect the controlled substances activity of the person or entity licensed.” – NASCSA, *NASCSA Membership* (2003) at <http://www.nascsa.org/membership.htm>.

¹⁸⁹John Burke Email, *supra* note 181.

¹⁹⁰Kathy Keough Interview, *supra* note 183.

¹⁹¹John Burke Email, *supra* note 181; Kathy Keough Interview, *supra* note 183.

¹⁹²David Folken Email, *supra* note 53.

¹⁹³Kathy Keough Interview, *supra* note 183.

¹⁹⁴John Burke Email, *supra* note 181.

the conference, “The vast majority of the restrictions on Xyrem were already in place when we viewed the program. It was the most comprehensive program I have ever seen before, or since.”¹⁹⁵

As noted, the FDA Advisory Committee that recommended approval of Xyrem for the treatment of cataplexy related to narcolepsy also recommended that a risk management program be adopted before final approval for distribution.¹⁹⁶ FDA adopted this proposal and required minor changes to the risk management program proposed by Orphan at that meeting.¹⁹⁷

The final distribution and risk-management plan, called the “Xyrem Success Program,” took the following form:¹⁹⁸

Orphan’s sales representatives contact physicians who treat narcolepsy and cataplexy in order to apprise them of the clinical successes of the drug. Unlike normal sales visits, Orphan does not provide the physician with any samples. The sale representative then takes the doctor through Orphan’s “Physician Success Program,” a series of videos, brochures, and pamphlets describing the distribution process, dosing and administration of Xyrem, home storage and secure handling, and typical drug diversion schemes (in order to make the physicians aware and alert to the possibility and threat of Xyrem diversion).¹⁹⁹ Each physician then has to sign a statement saying he or she has reviewed the program with the sales representative and understands it.

¹⁹⁵ *Id.*

¹⁹⁶ Final Minutes of the Food and Drug Administration Peripheral and Central Nervous System Drug Advisory Committee of June 6, 2001 (available at <http://www.fda.gov/ohrms/dockets/ac/01/minutes/3754m1.htm>).

¹⁹⁷ Press Release, *supra* note 92.

¹⁹⁸ This description is taken largely from Patti Engel Testimony, *supra* note 185, with details confirmed through Telephone Interview with David Folken, Senior Corporate Communications Specialist, Orphan Medical, Inc. (Mar. 17, 2004).

¹⁹⁹ Some of the Physician Success Program materials are available at <http://www.fda.gov/cder/foi/label/2002/21196lbl.pdf>.

Once a physician determines that a Xyrem prescription is appropriate for a patient, the physician faxes a special prescription form (provided exclusively by the Orphan sales representative) to the special pharmacy. The pharmacy then conducts a check on the prescribing physician, utilizing DEA's National Technical Information Services ("NTIS") database to ensure that each physician has an active valid medical license, and also to ensure that that physician has current prescribing privileges which allow him or her to prescribe Schedule III medications in this country. As a backup check, the specialty pharmacy also checks with the appropriate state medical board to determine that there are no pending actions on behalf of the state for that given physician.

The pharmacy then calls the prescribing physician's office to determine that the patient is real and that a prescription has in fact been written for that patient. At the pharmacy, each patient is assigned a dedicated pharmacy team who deals with that patient for the duration of the prescription – this allows the patient to not only get to know and trust the pharmacists, but also allows the pharmacy to more carefully monitor refill frequency and other tell-tale signs of diversion or abuse. Once insurance reimbursement is obtained, the pharmacy contacts the patient to determine patient's location and availability for shipment, and also to describe the contents of the shipment. These contents include not only the drug product, but also educational material – Orphan's "Patient Success Program" – videos, pamphlets, and brochures, designed for patients that describe the distribution process, dosing and administration information, information on home storage and handling as well as the criminal and civil penalties assigned to the illicit use of Xyrem, and contact information for the specialized pharmacy.²⁰⁰

The shipment is then sent utilizing the Rapid Trac System, a unique tracking system that allows real-time

²⁰⁰Some of the materials from the Patient Success Program are available at <http://www.fda.gov/cder/foi/label/2002/21196lbl.pdf>.

tracking of the package and delivery only upon an authorized signature by the patient or his or her designee (arranged ahead of time with the pharmacy). The deliverer makes only one redelivery attempt if the patient or designee is not available for delivery so as to minimize the time the drug is sitting in a warehouse or on a delivery truck and thus minimize the chance for diversion. Once the Rapid Trac System shows that delivery has occurred, specialty pharmacist call the patient within 24 hours to confirm receipt of the package and again reiterate the information and warnings about home storage and handling, as well as the penalties for illicit use.

Post-Approval

The one consistent critic of Xyrem, the approval process, and the risk management program, is Trinka Poratta, the director of ProjectGHB.org.²⁰¹ The website is dedicated to educating the public about the dangers of GHB, preventing GHB abuse, and providing a forum for recovering GHB-abusers and victims of GHB-related date-rapes to share stories and warn others of the dangers posed by the drug.²⁰² Ms. Poratta, a former LAPD officer who testified before both Congress and the FDA Advisory Committee, claims, among other things, that “FDA was bought and paid for by Orphan,”²⁰³ that the risk management program is a case of “the fox guarding the hen house,”²⁰⁴ that Orphan is pushing the off-label use of Xyrem,²⁰⁵ that many Orphan “investors are GHB addicts/pushers,”²⁰⁶ and that the only patients pushing for approval were paid for by Orphan and most are not interested in the drug.²⁰⁷ Orphan responds to these allegations

²⁰¹Comprehensive document research, as well as interviews with representatives from Orphan, NADDI, NASCSA, Narcolepsy Network, and the US Congress, did not reveal any other critics of the drug or its approval with the required restrictions.

²⁰²Project GHB, *About*, at <http://www.projectghb.org/about.htm>.

²⁰³E-mail from Trinka Poratta, Director, Projectghb.org, to Ariel Neuman, Student, Harvard Law School (Feb. 18, 2004, 21:20:26 PST) (on file with author).

²⁰⁴*Id.*

²⁰⁵*Id.*

²⁰⁶*Id.*

²⁰⁷E-mail from Trinka Poratta, Director, Projectghb.org, to Ariel Neuman, Student, Harvard Law School (Feb. 18, 2004, 15:21:23 PST) (on file with author).

by saying that “we have conducted and provided years of clinical research which has been evaluated by numerous experts in the field and obviously by FDA and they have clearly felt that Xyrem is a safe and effective medication when used appropriately. Law enforcement experts have been extremely supportive of our system and efforts. We’ve taken a very responsible approach in making sure this medicine is used appropriately and believe that her allegations are off-base.”²⁰⁸ John Burke of NADDI says that Ms. Poratta is unwilling to admit that her predictions “turned out to be incorrect,” and characterized her as a “zealot when it comes to GHB.”²⁰⁹ NASCSA Executive Director Kathy Keough, to whose organization Ms. Poratta made a presentation on GHB and “club drugs” to its members, characterized Ms. Poratta as an “extremist” with “blinders on” who “didn’t even want to imagine possibly that a company could try and do the right thing.”²¹⁰ Indeed, upon request Ms. Poratta could not provide any information which could be confirmed in order to back up her claims.²¹¹

Instead, according to almost all interested parties the Xyrem risk management program has in fact been a success. Since success in this instance is defined, as it was beginning with the Date-Rape Prohibition Act, as preventing diversion while allowing appropriate patient access, the fact that both law enforcement and patient advocates laud the system is a telling sign that the program is working. This does not, of course, mean that the fight against abuse of non-pharmaceutical GHB has been won; the number of emergency room visits involving GHB or GBL from industrial or other sources continues to rise every year as abuse continues to grow.²¹² However, according to John Burke, vice-president of the NADDI, Orphan’s risk management

²⁰⁸David Folken Email, *supra* note 53.

²⁰⁹John Burke Email, *supra* note 181.

²¹⁰Kathy Keough Interview, *supra* note 183.

²¹¹While one must note that almost all of the information available on Xyrem, its approval process, and the Congressional legislation is from sources whom Ms. Poratta criticizes and regards as untrustworthy, this is largely because she has criticized almost every party involved in the process. Although she seems to be the lone critic of Xyrem, Orphan, and the FDA in this instance, and despite her apparent lack of credibility on this issue, her work related to educating the public about the dangers of GHB and her attempts to prevent abuse of the drug are lauded by Orphan, NADDI, and NASCSA. Because of the prominent role she played in the debate over the approval of Xyrem, and because of her status as the sole critic, it is important to at least note her objections and criticisms.

²¹²National Drug Intelligence Center, US Dept. of Justice, *Information Bulletin: GHB Analogs* (August 2002) at <http://www.usdoj.gov/ndic/pubs1/1621/index.htm>.

“program is a success. It appears that only legitimate patients are receiving the drug, I know of no diversion incidents, or if there have been, extremely rare. I attribute (the success) primarily to the company’s efforts in setting up the program. . . it is an extraordinary program.”²¹³ Kathy Keough, Executive Director of NASCSA, says that she also has “not heard of a single case where there has been pharmaceutical grade GHB ending up on the street.” She attributes this largely to the success of the risk management program.²¹⁴ Indeed, Ms. Keough states that although she and her organization often pick up “rumblings” off the street before a larger drug abuse problem explodes, NASCSA is hearing nothing regarding any potential diversion of Xyrem.²¹⁵ The program’s unique features allows for identification of any type of unusual behavior, such as duplicate prescriptions, attempts at over-prescribing, or any attempts at over-use by the patient. The Rapid Trac System allows investigators to pinpoint the moment and location where a package is lost, if such an event were to occur.²¹⁶ At the same time, according to Bob Cloud, former Director of the Narcolepsy Network,²¹⁷ “people are getting the medication they need.”²¹⁸ This assessment is supported by the continually growing number of patients receiving Xyrem, which by November 2003 had reached 3,488 in just over a year.²¹⁹

Moreover, the numbers further undermine Ms. Poratta’s claims. Within a year of Xyrem’s commercial launch, 9,236 monthly prescriptions had been shipped, 15,758 prescription bottles had been shipped, and there had been six identified physician incidents and nine identified patient incidents.²²⁰ The physician

²¹³John Burke Email, *supra* note 181.

²¹⁴Kathy Keough, *supra* note 183.

²¹⁵*Id.*

²¹⁶Patti Engel Testimony, *supra* note 185.

²¹⁷The Narcolepsy Network is an organization whose membership is comprised of “people who have narcolepsy or related sleep disorders, such as Idiopathic Hypersomnia, their families and friends, and professionals involved in treatment, research, and public education regarding narcolepsy.” – Narcolepsy Network, *Narcolepsy Network, Inc.* at <http://www.narcolepsynetwork.org>.

²¹⁸Bob Cloud Interview, *supra* note 19.

²¹⁹Press Release, Orphan Medical, Inc., Orphan Medical Issues Record Xyrem® Prescriptions Update (Nov. 20, 2003) available at <http://www.orphan.com/articledetail.cfm?aid=4&id=420>.

²²⁰NASCSA held an educational conference in October 2003. At that conference, Pam Stahl, Orphan’s Vice President of Commercial Operations, gave a presentation on the company’s experience with Xyrem-related incidents in the year since the drug’s commercial launch. Pam Stahl, Presentation to NASCSA 2003 Conference (Oct. 21-25, 2003), at

incidents included four prescribing physicians who lacked the appropriate DEA license, and two people posing as physicians.²²¹ The patient incidents included one sexual assault of a medicated patient by a family member,²²² one accidental overdose,²²³ three cases of misuse/abuse,²²⁴ and four cases of lost or stolen products.²²⁵ During the same period 148 new prescriptions were cancelled because the Pharmacy could not contact the patient, 37 new prescriptions were put on hold because the Pharmacy could not contact patient, and 32 prescription refills were cancelled because the Pharmacy could not contact patient.²²⁶ Kathy Keough, Executive Director of NASCSA, evaluated these numbers as evidence that Orphan was doing a “fantastic job ensuring that (Xyrem) does not end up on the street.”²²⁷

The question as Orphan moves forward is whether it can sustain its success at keeping diversion incidents at or close to zero. Orphan continues its exploration into using Xyrem as a treatment for daytime sleepiness in narcolepsy patients,²²⁸ though this would still keep the number of patients being prescribed Xyrem fairly small. More worrisome for some of those concerned with possible diversion is Xyrem, Orphan is currently exploring submitting an IND to FDA to study Xyrem as a treatment for fibromyalgia.²²⁹ Fibromyalgia is estimated to afflict about 2% of the general population,²³⁰ meaning that if approved, Xyrem would

<http://www.nascsa.org/confer2003.htm>.

²²¹ *Id.*

²²² Patient moved to new home and continues to take Xyrem.

²²³ The overdose was traced to a broken piba dispenser on the prescription bottle, and the dispenser was subsequently redesigned by Orphan.

²²⁴ All of the patients' prescriptions were discontinued.

²²⁵ One package disappeared after being left at a house without the FedEx deliverer obtaining a signature, another disappeared after being mistakenly left in a hotel room, another was stolen after the patient's car was broken into, and a fourth was mistakenly discarded by a hospital pharmacy that was treating a patient for unrelated medical needs and was charged with dispensing all of his medication, including Xyrem. All four patients who reported these incidents were allowed to continue their prescriptions but under monitoring by the Pharmacy, with no further incidents reported for any of them. – Pam Stahl, Presentation to NASCSA 2003 Conference (Oct. 21-25, 2003), at <http://www.nascsa.org/confer2003.htm>.

²²⁶ *Id.*

²²⁷ Kathy Keough Interview, *supra* note 183.

²²⁸ National Institute of Health, *Trial Comparing Effects of Xyrem taken Orally and Modafinil with Placebo in Treating Daytime Sleepiness in Narcolepsy* (April 14, 2004), at <http://www.clinicaltrials.gov/ct/show/NCT00066170?order=1>.

²²⁹ *Xyrem Assessed as Treatment for Symptoms of Fibromyalgia Syndrome*, DRUG WEEK, Oct. 3, 2003, at 138. Fibromyalgia syndrome is a widespread musculoskeletal pain and fatigue disorder for which the cause is still unknown. Fibromyalgia means pain in the muscles, ligaments, and tendons – the soft fibrous tissues in the body. – Fibromyalgia Network website accessed at <http://www.fnnetnews.com/pages/basics.html>

²³⁰ Dayton Reardon Interview, *supra* note 46.

theoretically be available to a much larger segment of the population than the .05% affected by narcolepsy. If Orphan were able to maintain the Xyrem Success Program in the face of this potential increase in prescription volume, neither representatives of NADDI or NASCSA fear that diversion would increase.²³¹ At the same time, the question exists as to whether such a small company would be able to continue such restricted distribution on a larger scale.²³² The system is extraordinarily expensive – indeed, neither Xyrem nor Orphan as a whole have yet proved profitable, in large part because of the costs of the risk management program (though also due to ongoing clinical costs for Xyrem and Orphan’s other drug products).²³³ According to Orphan, while “the current system would be a possibility for the eventual approval and subsequent distribution of Xyrem for a fibromyalgia indication,”²³⁴ even the company admits that most likely if it “ever gets into a big market the central distribution is going to change.”²³⁵ The company treats this as a “bridge to cross in the future,”²³⁶ and a decision that will require further discussion both internally and with FDA.²³⁷ Nonetheless, Orphan’s plan is to always at least continue the physician and patient registry in order to be able to identify potential abusers, physician-impersonators, and doctor-shopping.²³⁸ At the same time, the concerns about GHB abuse and diversion have not abated, and winning approval from FDA, DEA, and others to change its distribution system may in fact be more difficult than Orphan would like to think.²³⁹

Conclusion

²³¹Kathy Keough Interview, *supra* note 183; John Burke E-mail, *supra* note 181.

²³²Kathy Keough Interview, *supra* note 183.

²³³David Folken Email, *supra* note 53.

²³⁴*Id.*

²³⁵Bob Cloud Interview, *supra* note 19.

²³⁶*Id.*

²³⁷David Folken Email, *supra* note 53.

²³⁸Bob Cloud Interview, *supra* note 19.

²³⁹See, e.g. 68 FR 66048-66052, proposed rulemaking by DEA for “additional recordkeeping and reporting requirements for drug products containing” GHB.

In the end, GHB's path to legitimacy is the story of government agencies, the US Congress, patient groups, and a good corporate citizen, working together to make sure citizens are both protected and treated. Along the way all sides were forced to compromise, but the compromises resulted in programs that are keeping pharmaceutical grade GHB off the street while ensuring that patients get the treatment they need. This is an instance where politics, law enforcement, and medicine had the opportunity to collide, but instead melded into a useful structure that satisfied almost all parties involved. As Orphan moves forward with its studies and hopes for wider distribution, one can only hope that the system continues to operate as smoothly and productively as it has thus far.²⁴⁰

²⁴⁰Note: Orphan recently announced that it had licensed the European sales and marketing rights to Celltech Pharmaceuticals, Inc. Press Release, Orphan Medical, Inc., Orphan Medical Licenses European Sales And Marketing Rights For Xyrem® To Celltech Pharmaceuticals, (Oct. 30, 2003) *available at* <http://www.orphan.com/articledetail.cfm?aid=4&id=417>.

According to Celltech, "GHB has been scheduled by the International Narcotics Control Board (<http://www.incb.org>) as a schedule 4 drug, and this is also the classification it has received from the European member states.

"In the UK, GHB represents a Schedule IV part I substance. Written Home Office authority is required to produce, supply or possess Schedule IV Part I drugs. Licenses are required for the import and export of Schedule 4 Part I drugs. Records of the supply and distribution of GHB must be kept and preserved, and also records of destruction must be kept and preserved by the license holder. Schedule IV Part I substances do not require handwritten prescriptions nor are subject to safe custody requirements.

"Since Xyrem (sodium oxybate) has not yet been submitted to the EMEA for central regulatory review, we do not know whether any additional restrictions to the above will be placed on the product by the EMEA itself, or by the members states. A pan-European license will be granted to Xyrem upon approval of the Marketing Authorization Application. As National legislation controlling the supply and distribution of controlled substances varies, the European Commission may apply some standard measures, but as Xyrem represents the first Controlled substance to be reviewed via the Centralized Procedure, it is not possible to predict whether National levels of control will be considered adequate.

"GHB was assigned a Schedule IV substance by the 32nd WHO Expert Committee on Drug dependence, and thus the National levels of control applicable to Schedule IV substances will apply."

– E-mail from Elanor Hunt, Business Development Manager, Celltech Pharmaceuticals, to Ariel Neuman, Student, Harvard Law School (Mar. 15, 2004, 17:13:11 GMT) (on file with author).