Jazz Pharmaceuticals®

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BY HAND DELIVERY

Division of Dockets Management
United States Food and Drug Administration
5630 Fishers Lane
Rm. 1061, HFA-305
Rockville, MD 20852

Docket No._____

CITIZEN PETITION

Petitioner Jazz Pharmaceuticals, Inc. (Jazz) hereby submits this Citizen Petition under section 505 of the Federal Food, Drug and Cosmetic Act (FDCA) and in accordance with 21 C.F.R. § 10.30 to request that the Commissioner of Food and Drugs take the actions described below. Jazz markets XYREM® (sodium oxybate) oral solution (hereinafter, Xyrem) which is indicated for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy.

I. ACTIONS REQUESTED

Jazz respectfully requests that the Food and Drug Administration (FDA) take the following actions:

1. Immediately publish in the Orange Book[1] bioequivalence requirements specifying whether *in vitro* or *in vivo* bioequivalence studies, or both such studies, are required for abbreviated new drug applications (ANDAs) referencing Xyrem (sodium oxybate) oral solution.

2. Not accept for review, review, or approve any ANDA referencing Xyrem (sodium oxybate) oral solution unless and until FDA has published bioequivalence requirements in the Orange Book specifying whether *in vitro* bioequivalence studies, *in vivo* bioequivalence studies, or both such studies, are required for ANDAs referencing Xyrem (sodium oxybate) oral solution.

[1] Officially, FDA's publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (32d ed. 2012) [hereinafter, *Orange Book*].

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3. Require *in vivo* bioequivalence studies, including fasted and fed bioequivalence studies and a demonstration of onset of drug action equivalent to Xyrem (sodium oxybate) oral solution, for any sodium oxybate drug product for which approval is sought in an ANDA referencing Xyrem (sodium oxybate) oral solution to the extent such sodium oxybate drug product differs from Xyrem in manufacturing process, pH, excipients, impurities, degradants or contaminants.[2]

II. STATEMENT OF GROUNDS

A. BACKGROUND

1. Sodium Oxybate / Gamma-Hydroxybutyrate

The active ingredient in Xyrem is sodium oxybate, which is the sodium salt of gamma-hydroxybutyrate (GHB). Sodium oxybate (SXB) has the molecular formula $C_4H_7NaO_3$, and its molecular weight is 126.09 grams/mole. GHB is an endogenous compound with hypnotic properties that is found in many human body tissues including in the central nervous system (CNS) and peripheral tissue.[3] It is also a minor metabolite and precursor of the major inhibitory neurotransmitter gamma-aminobutyric acid (GABA).[4] GHB is also the pharmacologically active metabolite of both gamma-butyrolactone (GBL)[5] and 1,4-BD[6], both of which are also used as agents of abuse.[7]

GHB has weak agonist activity at GABA(B) receptors and there appears to be a distinct GHB

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[2] FDA issues substantive responses to petition requests "relat[ing] to general standards for approval (e.g., bioequivalence criteria for generic drug products . . .)" even though they "may pertain to one or more pending drug applications." FDA, CENTER FOR DRUG EVALUATION AND RESEARCH, GUIDANCE FOR INDUSTRY, CITIZEN PETITIONS AND PETITIONS FOR STAY OF ACTION SUBJECT TO SECTION 505(q) OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT, p. 13, n. 18 (Jun. 2011), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079353.pdf. The Actions Requested here are exactly of the type described by FDA as deserving of a substantive response; it would therefore be arbitrary and capricious for FDA to deny them without a substantive response.

[3] Roth RH, Giarman NJ. Natural occurrence of gamma-hydroxybutyrate in mammalian brain. *Biochem Pharmacol.* 1970 March;19(Supp. 1):1087-93. *Exhibit 1.*

[4] Maitre M. The gamma-hydroxybutyrate signaling system in brain: organization and functional implications. *Prog Neurobiol.* 1997 Feb;51(3):337-61. *Exhibit 2.*

[5] Goodwin AK, Brown PR, Jansen EE, Jakobs C, Gibson KM, Weerts EM. Behavioral effects and pharmacokinetics of gamma-hydroxybutyrate (GHB) precursors gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD) in baboons. *Psychopharmacology (Berl).* 2009 Jun;204(3):465-76. *Exhibit 3.*

[6] Thai D, Dyer JE, Jacob P, Haller CA. Clinical pharmacology of 1,4-butanediol and gamma-hydroxybutyrate after oral 1,4-butanediol administration to healthy volunteers. *Clin Pharmacol Ther.* 2007 Feb;81(2):178-84. *Exhibit 4.*

[7] Lenz D, Rothschild MA, Kröner L. Intoxications due to ingestion of gamma-butyrolactone: organ distribution of gamma-hydroxybutyric acid and gamma-butyrolactone. *Ther Drug Monit.* 2008 Dec;30(6):755-61. *Exhibit 5.*

receptor site in the brain.[8] GHB dose-dependently alters dopaminergic activity; at sub-anesthetic doses there is an initial excitation of dopamine neurons producing elevated levels of synaptic dopamine.[9] At anesthetic doses, GHB blocks impulse flow from dopamine neurons, resulting in a build-up of dopamine in the nerve terminals.[10]

The pharmacological effect of GHB mimics natural physiological sleep, enhances REM sleep, and increases stages 3 and 4 of slow-wave sleep.[11] GHB decreases alcohol consumption and intensity of withdrawals.[12] Beyond its CNS effects, GHB has significant cardiovascular pharmacology and can cause bradycardia and dysregulation of blood pressure (hyper- and hypotension).[13]

GHB and GBL are subject to interconversion in aqueous solution. GBL is converted to GHB via hydrolysis; GHB is converted to GBL via intramolecular esterification.[14]

SXB is a hydrophilic compound with an apparent volume of distribution averaging 190-384 mL/kg[15] and an absolute bioavailability of 88%.[16] At SXB concentrations ranging from 3 to 300 mcg/mL, less than 1% is bound to plasma proteins.[17]

SXB is rapidly, but incompletely, absorbed after oral administration of Xyrem; absorption is delayed and decreased by a high fat meal.[18] It is eliminated mainly by metabolism with a half-

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[8] Molnár T, Antal K, Nyitrai G, Emri Z. Gamma-Hydroxybutyrate (GHB) induces GABA(B) receptor independent intracellular Ca2+ transients in astrocytes, but has no effect on GHB or GABA(B) receptors of medium spiny neurons in the nucleus accumbens. *Neuroscience*. 2009 Aug 18;162(2):268-81. *Exhibit 6.*

[9] Felmlee MA, Roiko SA, Morse BL, Morris ME. Concentration-effect relationships for the drug of abuse gamma-hydroxybutyric acid. *J Pharmacol Exp Ther*. 2010 Jun;333(3):764-71. *Exhibit 7.*

[10] Laureen J. Marinetti, *γ-Hydroxybutric Acid and Its Analogs, γ-Butyrolactone and 1,4-Butanediol in* BENZODIAZEPINES AND GHB: DETECTION AND PHARMACOLOGY Ch. 6, 95-126 (Salvatore J. Salamone ed., 2010). *Exhibit 8.*

[11] Boscolo-Berto R, Viel G, Montagnese S, Raduazzo DI, Ferrara SD, Dauvilliers Y. Narcolepsy and effectiveness of gamma-hydroxybutyrate (GHB): A systematic review and meta-analysis of randomized controlled trials. *Sleep Med Rev*. 2011 Nov 3. *Exhibit 9.*

[12] Leone MA, Vigna-Taglianti F, Avanzi G, Brambilla R, Faggiano F. Gamma-hydroxybutyrate (GHB) for treatment of alcohol withdrawal and prevention of relapses. *Cochrane Database Syst Rev*. 2010 Feb 17;(2):CD006266. *Exhibit 10.*

[13] DOT & NHTSA, Drugs and Human Performance Fact Sheets, REP. NO. DOT HS 809 725, pp. 3-5, 39-43, 97-100 (Apr. 2004). *Exhibit 11.*

[14] Ciolino LA, Mesmer MZ, Satzger RD, Machal AC, McCauley HA, Mohrhaus AS. The chemical interconversion of GHB and GBL: forensic issues and implications. *J Forensic Sci*. 2001;46(6):1315–1323. *Exhibit 12.*

[15] Xyrem® Package Insert, p. 2 (Nov. 18, 2005).

[16] FDA, CENTER FOR DRUG EVALUATION AND RESEARCH, Jazz Briefing Information, Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee, p. 24 (Aug. 20, 2010) [hereinafter, *Joint Ad. Comm. Briefing Information*]. *Exhibit 13*; *see also* eMC, Summaries of Product Characteristics for Xyrem®, Section 5.2: Pharmacokinetic Properties, *available at* http://www.medicines.org.uk/EMC/medicine/17364/SPC/Xyrem+500+mg+ml+oral+solution/. *Exhibit 14.*

[17] *See Joint Ad. Comm. Briefing Information* at 24.

[18] Borgen LA, Okerholm R, Morrison D, Lai A. The influence of gender and food on the pharmacokinetics of sodium oxybate oral solution in healthy subjects. *J Clin Pharmacol*. 2003 Jan;43(1):59-65. *Exhibit 15.*

life of 0.5 to 1 hour.[19] Pharmacokinetics are nonlinear with blood levels increasing 3.7-fold as dose is doubled from 4.5 to 9 grams (g).[20]

2. Xyrem is a Controlled Substance

GHB is a Schedule I controlled substance.[21] Schedule I is reserved for controlled substances that have a high potential for abuse, have no currently accepted medical use in treatment in the U.S., and for which there is a lack of accepted safe use under medical supervision.[22] GHB became a Schedule I controlled substance based on its abuse as a recreational drug and its association with a number of drug-facilitated sexual assaults.[23]

Unlike GHB, Xyrem is a Schedule III controlled substance.[24] This bifurcated schedule is unusual and the product of an act of Congress.[25] Schedule III substances have a currently accepted medical use in treatment in the United States and are considered to have less potential for abuse than the drugs or other substances in Schedules I and II.[26]

3. Xyrem Has Unique Safety Concerns

FDA approved Xyrem first in 2002 for the treatment of cataplexy in patients with narcolepsy and again in 2005 for the treatment of excessive daytime sleepiness in patients with narcolepsy.[27] Xyrem was developed at the urging of FDA, which was seeking therapeutic options for orphan

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[19] Brenneisen R, Elsohly MA, Murphy TP, Passarelli J, Russmann S, Salamone SJ, Watson DE. Pharmacokinetics and excretion of gamma-hydroxybutyrate (GHB) in healthy subjects. *J Anal Toxicol.* 2004 Nov-Dec;28(8):625-30. *Exhibit 16.*

[20] Xyrem® Package Insert, p. 2 (Nov. 18, 2005).

[21] DEA, News Release, GHB Added to the List of Schedule I Controlled Substances (Mar. 13, 2000), *available at* http://www.justice.gov/dea/pubs/pressrel/pr031300.htm. *Exhibit 17.*

[22] *See* 21 U.S.C. § 812(b)(1).

[23] DEA, News Release, Gamma Hydroxybutryic Acid (GHB, liquid X, Goop, Georgia Home Boy) (Mar. 13, 2000) ("The 'Hillary [*sic*] Farias and Samantha Reed Date-Rape Prohibition Act of 1999' (Public Law 106-172) was signed on February 18, 2000. On that date, GBL became a List I chemical, subject to the criminal, civil and administrative sanctions of the Controlled Substances Act. On March 13, 2000, GHB was made a Schedule I controlled substance (65 FR 13235-13238). Therefore, effective on that date, GHB became subject to the regulatory controls and the criminal, civil and administrative sanctions of the Controlled Substances Act as a Schedule I controlled substance."), *available at* http://www.justice.gov/dea/pubs/pressrel/pr031300_01.htm. *Exhibit 18.*

[24] Xyrem® Package Label, p. 20 (Nov. 18, 2005).

[25] Hillory J. Farias and Samantha Reid Date-Rape Drug Prohibition Act of 2000, Pub. L. No. 106-172, 114 Stat. 7 (2000).

[26] DOJ & DEA, DRUGS OF ABUSE, p. 9 (2011 ed.), *available at* http://www.justice.gov/dea/pubs/drugs_of_abuse.pdf. *Exhibit 19.*

[27] Letter from Russell Katz, Dir. Division of Neurology Products, CDER to Orphan Medical, sNDA Approval Letter for Xyrem, NDA 21-196/S-005 (Nov. 18, 2005) [hereinafter, *Xyrem Approval Letter #2*]; Letter from Robert Temple, Dir. Office of Drug Evaluation, CDER to Orphan Medical, Approval Letter for Xyrem, NDA 21-196 (Jul. 17, 2002) [hereinafter, *Xyrem Approval Letter #1*].

diseases like narcolepsy.[28] Narcolepsy is a debilitating disease, and challenging for many patients to manage. Today, SXB is considered by the American Academy of Sleep Medicine to be a standard of care for the treatment of cataplexy and excessive daytime sleepiness.[29]

At the same time, abuse of illicit GHB has been a serious issue. Abuse of GHB also has been associated with some important CNS adverse events (including death). GHB intoxication is considered a significant cause of morbidity and mortality in those abusing the drug for recreational purposes.[30] Symptoms of GHB poisoning are characterized as dose-dependent and partly similar to those of alcohol poisoning.[31] Moreover, GHB's association as a "date-rape" drug led Congress to legislatively bifurcate illicit GHB as a Schedule I substance but permit FDA approval of Xyrem as a Schedule III prescription drug product.

Even at recommended doses, SXB use has been associated with confusion, depression, and other neuropsychiatric events.[32] Furthermore, in sensitive individuals, even at normal therapeutic doses, GHB has the potential to induce life-threatening respiratory depression.[33] Currently there are no available therapeutic interventions for the treatment of a GHB overdose.[34] Patients receiving Xyrem-based therapy often exhibit other severe clinical manifestations and illness, and as such are at higher risk than the general population for negative health outcomes.[35]

Xyrem also carries labeling stating that the product has CNS depressant effects and has been associated with confusion, depression, and other neuropsychiatric events.[36] The CNS depressant effects of SXB have the potential to cause respiratory depression and decreases in the level of consciousness, including rare instances of coma[37] and death.[38]

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[28] *See* FDA, CENTER FOR DRUG EVALUATION AND RESEARCH, Orphan Medical Presentation, Meeting of the Pediatric Subcommittee of the Peripheral and Central Nervous System Drug Advisory Committee, p. 5 (Jun. 6, 2001). *Exhibit 20.*

[29] Morgenthaler TI, Kapur VK, Brown T, Swick TJ, Alessi C, Aurora RN, Boehlecke B, Chesson AL Jr, Friedman L, Maganti R, Owens J, Pancer J, Zak R. Standards of Practice Committee of the American Academy of Sleep Medicine. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. *Sleep.* 2007 Dec; 30(12): 1705-11. *Exhibit 21.*

[30] Okun MS, Boothby LA, Bartfield RB, Doering PL. GHB: an important pharmacologic and clinical update. *J Pharm Pharm Sci.* 2001 May-Aug;4(2):167-75. *Exhibit 22.*

[31] Andresen H, Aydin BE, Mueller A, Iwersen-Bergmann S. An overview of gamma-hydroxybutyric acid: pharmacodynamics, pharmacokinetics, toxic effects, addiction, analytical methods, and interpretation of results. *Drug Test Anal.* 2011 Sep;3(9):560-8. *Exhibit 23.*

[32] Xyrem® Package Insert, p. 1 (Nov. 18, 2005).

[33] Wang YG, Swick TJ, Carter LP, Thorpy MJ, Benowitz NL. Sodium oxybate: updates and correction to previously published safety data. *J Clin Sleep Med.* 2011 Aug 15;7(4):415-6). *Exhibit 24.*

[34] Felmlee MA, Krzyzanski W, Morse BL, Morris ME. Use of a local sensitivity analysis to inform study design based on a mechanistic toxicokinetic model for γ -hydroxybutyric acid. *AAPS J.* 2011 Jun;13(2):240-54. *Exhibit 25.*

[35] Roth T, Bogan RK, Culpepper L, Doghramji K, Doghramji P, Drake C, Grauke JH, Knoepflmacher P, Sateia M, Silvershein D, Thorpy MJ. Excessive sleepiness: under-recognized and essential marker for sleep/wake disorder management. *Curr Med Res Opin.* 2010 Dec;26 Suppl 2:S3-24. *Exhibit 26.*

[36] Xyrem® Package Insert, p. 1 (Nov. 18, 2005).

[37] *Id.*; Centers for Disease Control and Prevention (CDC). Gamma hydroxy butyrate use--New York and Texas, 1995-1996. *MMWR Morb Mortal Wkly Rep.* 1997 Apr 4;46(13):281-3. *Exhibit 27.*

[38] Xyrem® Package Insert, p. 1 (Nov. 18, 2005).

In order to gain approval for Xyrem, Jazz's predecessor addressed these concerns regarding misuse, abuse, diversion, and CNS adverse events by developing a closed-loop system that includes particularly restrictive controls on access. For example, Xyrem's labeling carries a boxed warning reiterating that GHB is a known drug of abuse with a high potential for toxicity. Boxed warnings are reserved for drugs associated with "[c]ertain contraindications or serious warnings, particularly those that may lead to death or serious injury".[39]

Xyrem was also one of the few drugs deemed to have a Risk Evaluation and Mitigation Strategy (REMS) pursuant to the 2007 Food and Drug Administration Amendments Act (FDAAA).[40] A REMS is a strategy to manage a known or potential serious risk associated with a drug or biological product where FDA has determined that such a strategy is necessary to ensure the benefits of the drug or biological product outweigh its risks.[41] REMS can include several elements including medication guides, communication plans, and elements to assure safe use (ETASU). REMS with ETASU are typically the most restrictive REMS plans, reserved for drugs with significant safety concerns.[42]

4. Bioequivalence Requirements for Generic Copies of Xyrem

An ANDA seeks approval of a generic drug by referencing an innovator product, e.g., Xyrem, which previously "has been approved for safety and effectiveness under subsection (c)" of the Federal Food, Drug, and Cosmetic Act § 505.[43] The law refers to the referenced innovator product as a "listed drug" because FDA is required to publish all such drugs in a list, updated every thirty days.[44] FDA's regulations describe the listed drug on which an ANDA relies as a "Reference Listed Drug" (RLD).[45]

In addition to publishing listed drugs, the law also mandates that FDA publish "whether in vitro or in vivo bioequivalence studies, or both such studies, are required" for generic copies of each listed drug.[46] Accordingly, a generic applicant must submit information to FDA showing its generic product is bioequivalent to the listed drug it references.[47]

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[39] *See* 21 C.F.R. § 201.57(c)(1).

[40] *See* Identification of Drugs and Biological Products Deemed to Have Risk Evaluation and Mitigation Strategies (REMS) for Purposes of the Food and Drug Administration Amendments Act of 2007; Notice, 73 Fed. Reg. 16,313, 16,313-14 (Mar. 27, 2008). Other examples of products that were deemed to have a REMS are thalidomide, isotretinoin, and a small pox vaccine. *See id.*

[41] 21 U.S.C. § 355-1(a)(1); *see also, e.g.*, FDA, OFFICE OF DRUG SAFETY, DRAFT GUIDANCE FOR INDUSTRY, FORMAT AND CONTENT OF PROPOSED RISK EVALUATION AND MITIGATION STRATEGIES (REMS), REMS ASSESSMENTS, AND PROPOSED REMS MODIFICATIONS, p. 2 (Sep. 2009), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm184128.pdf, [hereinafter *REMS Guidance*].

[42] *REMS Guidance* at 11 ("Elements to assure safe use are intended to provide safe access for patients to drugs with known serious risks that would otherwise be unavailable.").

[43] 21 U.S.C. §§ 355(j)(2)(A)(i), (j)(7)(A)(i)(I).

[44] 21 U.S.C. §§ 355(j)(2)(A)(i), (j)(7)(A)(ii).

[45] 21 C.F.R. § 314.3(b).

[46] 21 U.S.C. § 355(j)(7)(A)(i)(III).

[47] 21 U.S.C. § 355(j)(2)(A)(iv).

FDA's regulations reiterate the law. They state that, "FDA may require in vivo or in vitro testing, or both, to...establish the bioequivalence of specific drug products."[48] The regulations further provide that FDA will meet the law's mandate to publish bioequivalence requirements for specific products by publishing such information in FDA's "Approved Drug Products With Therapeutic Equivalence Evaluations", also known as the Orange Book.[49] And the regulations define a "bioequivalence requirement" as "a requirement imposed by the Food and Drug Administration for in vitro and/or in vivo testing of specified drug products which must be satisfied as a condition of marketing."[50]

The regulations also state that FDA may "waive the submission of evidence demonstrating in vivo bioequivalence" and instead permit only *in vitro* bioequivalence studies.[51] The regulations enumerate various waivers of *in vivo* bioequivalence.[52] For oral solutions, FDA may waive the requirement of *in vivo* bioequivalence if the ANDA product contains an active ingredient "in the same concentration and dosage form" as the RLD, as well as data showing that the ANDA product:

> [c]ontains no inactive ingredient or other change in formulation from the [RLD]... that may significantly affect absorption of the active drug ingredient or active moiety for products that are systemically absorbed.[53]

Waiver under this provision is based on an FDA determination that a generic product's "in vivo...bioequivalence may be considered self-evident."[54]

B. ARGUMENT

FDA has not complied with the law's mandate to publish bioequivalence requirements specifying whether ANDA applicants seeking to copy Xyrem must conduct *in vivo* bioequivalence studies, *in vitro* bioequivalence studies, or both types of bioequivalence studies as a condition of obtaining FDA marketing approval. Until FDA rectifies its ongoing failure to comply with the law, no ANDAs purporting to copy Xyrem can be accepted for review, reviewed, or approved by FDA. Moreover, given the particularly serious risks associated with Xyrem, as well as recent science regarding mechanisms of GHB absorption from the gut, and manufacturing and excipient effects on drug absorption, when FDA does promulgate bioequivalence requirements for ANDAs that reference Xyrem, it should require *in vivo* fed and

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[48] 21 C.F.R. § 320.24(a).
[49] *Id.*
[50] 21 C.F.R. § 320.1(f); *see also* 21 C.F.R. 320.24(a) ("Applicants shall conduct bioavailability and bioequivalence testing using the most accurate, sensitive, and reproducible approach available...").
[51] 21 C.F.R. § 320.21(b)(2).
[52] *See generally* 21 C.F.R. § 320.22.
[53] 21 C.F.R. § 320.22(b)(3)(iii).
[54] 21 C.F.R. § 320.22(b).

fasted bioequivalence testing, unless the generic product is indistinguishable from Xyrem in terms of manufacturing process, pH, excipients, impurities, degradants and contaminants.

1. FDA Cannot Accept for Review, Review or Approve ANDAs Referencing Xyrem Unless and Until It Publishes Bioequivalence Requirements for Generic Copies of Xyrem in the Orange Book

The law required FDA to publish "whether in vitro or in vivo bioequivalence studies, or both such studies, are required" for generic copies of Xyrem within 30 days of Xyrem's approval in 2002.[55] FDA failed to do so. That failure has continued to the present date. FDA has therefore violated the FDCA and the Agency's own regulations.[56]

FDA's failure to establish bioequivalence requirements for generic copies of Xyrem also violates basic provisions of the Administrative Procedure Act. Congress required FDA to publish bioequivalence requirements for Xyrem generics within 30 days of Xyrem's 2002 approval, but ten years later FDA has yet to do so. FDA has therefore "unlawfully withheld" the legally required action of publishing bioequivalence requirements for Xyrem generics, and done so in a manner—a ten-year delay (and counting)—that "unreasonably delayed" that action.[57] FDA's action was "not in accordance with law," "in excess of statutory jurisdiction, authority, or limitations," "short of statutory right," and accomplished "without observance of procedure required by law."[58]

Here, the "procedure required by law" mandated that FDA publish bioequivalence requirements for Xyrem generics within 30 days of Xyrem's original approval date of July 17, 2002.[59] This is the same timeframe Congress mandated for FDA publication of Xyrem as an RLD in the Orange Book.[60] Thus, Congress, by law, instructed FDA to publish, by the same deadline, both new RLDs and the bioequivalence requirements a generic applicant seeking to copy each new RLD would have to meet.

Consequently, under the "procedure required by law," publication of bioequivalence requirements for a given RLD necessarily precedes the filing of any ANDA seeking to copy that RLD. The law requires that ANDAs must reference an RLD.[61] An RLD does not become an RLD until FDA identifies it as such in the statutorily mandated "list"—the Orange Book.[62] And since the law requires, by the same 30 day deadline as the listing of a new RLD, the publication of bioequivalence requirements for ANDAs seeking to copy that RLD, such bioequivalence requirements will always, under the statutory scheme enacted by Congress, be published prior to the filing of any ANDAs for a given RLD.

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[55] 21 U.S.C. § 355(j)(7)(A)(i)-(ii).
[56] 21 C.F.R. § 320.24(a).
[57] 5 U.S.C. § 706(1).
[58] 5 U.S.C. §§ 706(2)(A), (C)-(D).
[59] 21 U.S.C. § 355(j)(7)(A)(i)-(ii); *Xyrem Approval Letter #1.*
[60] *Id.*
[61] 21 U.S.C. §§ 355(j)(2)(A), (7)(A)(i); 21 C.F.R. § 314.94(a)(3).
[62] 21 C.F.R. § 314.3; *see also Orange Book* preface.

Here, by contrast, FDA has not followed the procedure required by law. As discussed, FDA did not publish bioequivalence requirements for Xyrem generics by the statutory deadline. And, in the fall of 2010, FDA accepted for review an ANDA seeking to copy Xyrem,[63] which ANDA evidently did not follow any statutorily mandated bioequivalence requirements for Xyrem, because FDA has failed to publish any. FDA's acceptance for review and actual review of this ANDA is therefore "agency action . . . without observance of procedure required by law," "not in accordance with law," "in excess of statutory jurisdiction, authority, or limitations," and "short of statutory right," and thus must be set aside.[64]

Any FDA action to accept for review, review, or approve any ANDA purporting to copy Xyrem will violate the law unless and until FDA has published bioequivalence requirements for such applications. Congress mandated that FDA publish bioequivalence requirements for ANDAs for each drug listed as an RLD, as discussed above. Thus Congress intended, and explicitly charged FDA to promulgate, bioequivalence requirements for each RLD. Bioequivalence requirements, it will be recalled, are indeed requirements—they "must be satisfied as a condition of marketing."[65]

While Congress mandated that there be bioequivalence requirements that must be satisfied as a condition of marketing Xyrem generics, FDA has not promulgated those requirements. As a result, FDA cannot accept sodium oxybate ANDAs for review, because it has no bioequivalence requirements against which to review them, and such ANDAs obviously cannot contain evidence purporting to satisfy requirements that do not exist. Similarly, FDA cannot review sodium oxybate ANDAs in the absence of both bioequivalence requirements for sodium oxybate generics and evidence contained in the ANDA purporting to demonstrate that the ANDA product meets those requirements, which are currently nonexistent. Nor can FDA presently approve sodium oxybate ANDAs, since approvals would require meeting bioequivalence requirements mandated by Congress, but said requirements have yet to be promulgated.

Furthermore, in the scenario where additional ANDAs from different manufacturers are reviewed and approved by FDA, the absence of bioequivalence requirements for Xyrem generics will permit variability among generic sodium oxybate products. Here again, FDA's approach violates the law. Congress mandated bioequivalence requirements, i.e., requirements "imposed by the Food and Drug Administration for in vitro and/or in vivo testing of specified drug products which must be satisfied as a condition of marketing."[66] The same bioequivalence requirements must therefore be met by all generic sodium oxybate products, thus enforcing uniformity across all versions of Xyrem. FDA's failure to promulgate bioequivalence requirements for generic versions of Xyrem opens the door to variability among sodium oxybate

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[63] Roxane Laboratories asserted to Jazz by letter dated October 14, 2010 that it had filed, and the FDA had received, an ANDA referencing Xyrem, which contained (1) "any required bioequivalence or bioavailability data or information"; and (2) a Paragraph IV certification with respect to certain Xyrem patents. *See* Letter from Randall S. Wilson, Vice President, Scientific, Medical and Regulatory Affairs, Roxane Laboratories, Inc. to Bruce C. Cozadd, Chairman and Chief Executive Officer, Jazz Pharmaceuticals, p. 1 (Oct. 14, 2010). *Exhibit 28.*

[64] 5 U.S.C. § 706(2)(A), (C)-(D).

[65] 21 C.F.R.§ 320.1(f).

[66] *Id.*

drug products that may be used by the same patient, which Congress did not intend, and, in legislative language, specifically precluded.[67]

Any ANDAs referencing Xyrem as a listed drug should not be accepted for review by FDA, and any such ANDAs currently pending should be refused further review and returned to their applicants. Unless and until FDA publishes bioequivalence requirements for generic copies of Xyrem in the Orange Book, ANDAs referencing Xyrem are not acceptable for review, not reviewable, and not approvable.[68]

2. Therapeutic Equivalence Evaluations Do Not Satisfy the Statutory Mandate to Publish Bioequivalence Requirements

FDA has recently stated that Orange Book "Therapeutic Equivalence Evaluations" fulfill FDA's statutory obligation to publish "whether in vitro or in vivo bioequivalence studies, or both such studies, are required" for generic copies of a given RLD within 30 days of the RLD approval.[69] Jazz respectfully disagrees and believes that the FDA should reconsider this statement, which was presented previously in the context of a different issue.

The statute mandates that FDA publish which types of bioequivalence studies are "required" for a given RLD, but Therapeutic Equivalence Evaluations in fact have no legal force and so cannot constitute requirements. As the Orange Book states, Therapeutic Equivalence Evaluations "are not official FDA actions affecting the legal status of products under the Act."[70] Rather, their function is "to serve as public information and advice to state health agencies, prescribers, and pharmacists to promote public education in the area of drug product selection and to foster containment of health care costs."[71] FDA actions that are "not official" and do not affect the legal status of products like generic versions of sodium oxybate cannot bind ANDA applicants, and hence cannot constitute publication of "whether in vitro or in vivo bioequivalence studies, or both such studies, are *required*"[72] for generic copies of Xyrem.

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[67] Jazz recognizes that FDA may take the position that bioequivalence showings can vary among different generic copies of the same RLD. That, however, is an insufficient basis to ignore the clear language of the law and leads to all of the problems discussed herein, which Congress never intended because it assumed, reasonably, that FDA would follow the law. *See, e.g., Household Credit Servs., Inc. v. Pfennig*, 541 U.S. 232, 239 (2004) (agencies must give effect to the unambiguously expressed intent of Congress); *Chevron, U.S.A., Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 842 (1984) (no deference is afforded to agency when "Congress has directly spoken to the precise question at issue").

[68] It may be contended that FDA has the discretion to determine whether bioequivalence requirements should exist for a given reference listed drug. That is not the case. FDA has no discretion whether/not to promulgate bioequivalence requirements. Congress, by law, required FDA by a particular deadline—within 30 days after approval of an NDA—to publish bioequivalence requirements for generic copies of the drug approved in the NDA. 21 U.S.C. § 355(j)(7)(A)(i)-(ii).

[69] Letter from Janet Woodcock, Dir., CDER to Thomas F. Doyle, ViroPharma, Inc., Docket No. FDA-2006-P-0007, p. 60 (Apr. 9, 2012) [hereinafter *Woodcock Letter*].

[70] *Orange Book* preface.

[71] *Id.*

[72] 21 U.S.C. § 355(j)(7)(A)(i)(III) (emphasis added).

It is also difficult to reconcile the backward-looking nature of Therapeutic Equivalence Evaluations with the statute's use of the present tense. Therapeutic Equivalence Evaluations issue only after approval of a generic copy of the given RLD.[73] A Therapeutic Equivalence Evaluation thus can only reveal whether *in vitro*, *in vivo*, or both types of bioequivalence studies *were* required for approval of a generic product already approved.[74] The statute, however, requires FDA to publish what bioequivalence studies "*are* required." By not publishing which bioequivalence studies "*are* required" for generic copies of Xyrem FDA is therefore presently in violation of the statute.

Not publishing bioequivalence requirements unless and until an ANDA has already been approved also adds an extra-statutory contingency to the law enacted by Congress. If Congress had intended publication of bioequivalence requirements only if and when ANDAs have already been approved, then Congress would have written the statute differently. For example, the statute could have been written with changes like these:

> [FDA shall publish] whether in vitro or in vivo bioequivalence studies, or both such studies, ~~are~~ were required for applications filed under this subsection if such applications have been submitted and approved . . .

This, however, is not the statute Congress enacted. The unambiguous statutory language is in the present tense, and mandates publication of bioequivalence requirements for each RLD *regardless of whether an ANDA has been submitted or approved for that RLD*. Because FDA's approach alters the clear wording enacted by Congress, it cannot stand.[75]

Delaying issuance of bioequivalence requirements unless and until ANDAs have been approved also fails to comply with the statutory mandate to publish bioequivalence requirements within 30 days of the given RLD's approval. The statute requires that "[e]very thirty days" FDA must update "the list [of RLD's] under clause (i)."[76] The cross-referenced clause (i) in turn requires publication of: (I) the official and proprietary name of each new drug approved for safety and effectiveness; (II) the new drug's date of approval and application number; "and (III) whether in vitro or in vivo bioequivalence studies, or both such studies, are required" for generic copies of the newly listed drug.[77]

FDA has stated that it complies with prongs one and two of this statutory triptych "at the time the NDA is approved or shortly thereafter"[78]—i.e., in a manner more or less compliant with the statute's 30 day deadline. But although prong three is explicitly conjoined ("and (III)") with its

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[73] *Woodcock Letter* at 60.
[74] *Id.*
[75] *See, e.g., Household Credit Servs., Inc. v. Pfennig*, 541 U.S. 232, 239 (2004) (agencies must give effect to the unambiguously expressed intent of Congress); *Chevron, U.S.A., Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 842 (1984) (no deference is afforded to agency when "Congress has directly spoken to the precise question at issue").
[76] 21 U.S.C. § 355(j)(7)(A)(ii).
[77] 21 U.S.C. § 355(j)(7)(A)(i)(I)-(III).
[78] *Woodcock Letter* at 60.

brethren, FDA has stated that it need not comply with the 30 day publication requirement when fulfilling prong three. Instead, according to FDA:

> The Agency fulfills the third prong of this statutory directive by including on the list of approved products a "therapeutic equivalence" code for each product once another product that is pharmaceutically equivalent to the listed product is approved.[79]

FDA has asserted the statute's language does not mandate publication of bioequivalence requirements at the same time as RLD listing,[80] but this does not address the question of whether the statutory 30 day deadline applies to publication of bioequivalence requirements. As explained above, the 30 day deadline applies to "clause (i)", which in turn requires publication of three things, the third being "whether in vitro or in vivo bioequivalence studies, or both such studies, are required".[81] This provision "direct[s] when FDA must fulfill this requirement" because, as FDA says, the statute does not otherwise do so.[82]

FDA has also cited a judicial decision.[83] That case, however, stands for a different proposition—that FDA has discretion regarding bioequivalence methods—and did not address whether FDA is required to publish "whether in vitro or in vivo bioequivalence studies, or both such studies, are required"[84] for generic copies of an RLD within 30 days of that RLD's approval, the issue here.

FDA has also expressed concern that the statutory 30 day deadline, if applied as written, would render superfluous "other provisions of section 505(j)".[85] But the example FDA cites to illustrate its point is a provision that simply requires FDA to meet with applicants who make a reasonable written request to discuss "the design and size of bioavailability and bioequivalence studies,"[86] *not* "whether in vitro or in vivo bioequivalence studies, or both such studies, are required."[87] These provisions are not in tension with each other. A determination whether *in vitro* or *in vivo* studies are required does not require determining the design and size of the studies.

Therapeutic Equivalence Evaluations themselves demonstrate this. Therapeutic Equivalence Evaluations do not discuss "the design and size of . . . bioequivalence studies", but nonetheless, according to FDA, they do fulfill the bioequivalence requirement publication mandate.[88] FDA undoubtedly could include specific protocol designs in the Orange Book if it so chose, but it is not required to do so by the statutory mandate at issue here, and thus the argument to superfluity fails.

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[79] *Id.*
[80] *Id.* at 61.
[81] 21 U.S.C. § 355(j)(7)(A)(i)(III).
[82] *Woodcock Letter* at 61.
[83] *Id.* at 61 n.281 (citing *Schering Corp. v. FDA*, 51 F.3d 390, 398 (3d Cir. 1995)).
[84] 21 U.S.C. § 355(j)(7)(A)(i)(III).
[85] *Woodcock Letter* at 61.
[86] 21 U.S.C. § 355(j)(3)(B).
[87] 21 U.S.C. § 355(j)(7)(A)(i)(III).
[88] *Woodcock Letter* at 60-61.

FDA is also concerned that compliance with the statute's 30 day publication mandate "would require the Agency to expend enormous resources to generate and evaluate the scientific data required to establish bioequivalence."[89] However, the statute does not require FDA to generate bioequivalence data, but only to publish "whether in vitro or in vivo bioequivalence studies, or both such studies, are required."[90] ANDA applicants must generate the data purporting to establish whether they meet those requirements, and it is undeniably FDA's province to evaluate whether such claims are accurate—FDA is already doing this work in the status quo. Thus FDA's concerns that compliance with the statutory 30 day publication deadline would be an "enormous" new burden do not, upon review, appear justified.

It also bears mention that the legislative history underscores Congress' intent to create "a program whereby *information about listed drugs which could be copied* would become available."[91] This statement confirms congressional intent to ensure ANDA applicants (and the general public) know about bioequivalence requirements before ANDAs are filed. By contrast, Congress did not say that it wanted a program whereby information about *only those* listed drugs *which have been copied* would become available *after ANDA approvals*. But such is the result triggered by FDA's delayed approach of not publishing bioequivalence requirements unless and until a generic has been approved.[92]

In conclusion, the statute plainly required issuance of bioequivalence requirements for generic versions of Xyrem within 30 days of Xyrem's approval, but this has yet to occur. By contrast, legally nonbinding Therapeutic Equivalence Evaluations issued years after RLD approval, and only if an ANDA is approved, cannot meet the statute's prospective mandate that for all RLDs FDA must publish, within 30 days of RLD approval, "whether in vitro or in vivo bioequivalence studies, or both such studies, are required."[93]

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[89] *Id.* at 61.

[90] 21 U.S.C. § 355(j)(7)(A)(i)(III).

[91] H.R. REP. NO. 98-857, pt. 2, at 17 (1984) (emphasis added). *Exhibit 29.*

[92] Indeed, multiple preamble statements reflect FDA's own recognition that publication of bioequivalence requirements was intended to guide prospective ANDA applicants, not serve as a backward look at what has been required for ANDAs already approved. E.g., "Section 505(j)(6) of the act directs the Secretary to publish a list of all approved drugs *for which ANDA's may be submitted* and to state 'whether in vitro or in vivo bioequivalence studies, or both such studies, are required * * *'". Abbreviated New Drug Application Regulations; Final Rule, 57 Fed. Reg. 17,950, 17,972 (Apr. 28, 1992) (emphasis added); "The list specifies *whether an in vitro or in vivo bioequivalence study will be required* for ANDA's that refer to a listed drug." Abbreviated New Drug Application Regulations; Proposed Rule, 54 Fed. Reg. 28,872, 28,882 (Jul. 10, 1989) (emphasis added); "The agency informs *prospective applicants* of *whether in vivo or only in vitro tests will be required* through its list." *Id.* at 28,883 (emphasis added). FDA does not seek to reconcile these statements with its position that Therapeutic Equivalence Evaluations issued after generic approvals somehow meet the statute's prospective, within-30-days-of-RLD-approval requirement.

[93] 21 U.S.C. § 355(j)(7)(A)(i)(III).

3. FDA Cannot Accept for Review, Review, or Approve ANDAs Referencing Xyrem Without Requiring *In Vivo* Bioequivalence Studies, *In Vitro* Bioequivalence Studies, or Both

Under the law, FDA has three options from which to choose when deciding what type of bioequivalence showing should be required for generic copies of a given reference listed drug. FDA can require *in vivo* bioequivalence studies.[94] It can require *in vitro* bioequivalence studies.[95] Or FDA can require both *in vivo* and *in vitro* bioequivalence studies.[96] The law does not permit FDA to accept any other showings of bioequivalence.

FDA's regulations provide, generally, that to demonstrate *in vivo* bioequivalence an applicant must show "the absence of a significant difference in the rate and extent to which the active [ingredient] becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study."[97] Various methods are possible for demonstrating *in vivo* bioequivalence, the most typical being a demonstration of comparable pharmacokinetic bioavailability. As discussed above, FDA has yet to specify which particular *in vivo* bioequivalence method is required for generic copies of Xyrem.

For applications requiring only *in vitro* bioequivalence studies, FDA's regulations provide for waiver of the *in vivo* showing of bioequivalence, as discussed above.[98] The regulations do not include provisions for waiver of *in vitro* bioequivalence studies. Thus, in the case of oral solutions, the waiver regulation provides for waiver of *in vivo* bioequivalence studies (the "drug product's *in vivo* . . . bioequivalence may be considered self-evident"[99]) under some circumstances; but nowhere do the regulations state that *in vitro* bioequivalence studies may also be waived. Nor could they, because the law mandates that FDA must require *in vivo*, *in vitro*, or both types of bioequivalence showings.[100]

In sum, when FDA engages in the process to determine what the bioequivalence requirements should be for generic copies of Xyrem, the law and regulations permit *in vivo* bioequivalence study requirements, *in vitro* study requirements, or both, but not neither.

4. FDA Should Require *In Vivo* Bioequivalence Studies for all Sodium Oxybate ANDAs that Differ From Xyrem in Manufacturing Process, pH, Excipients, Impurities, Degradants or Contaminants

The serious risks associated with Xyrem—sufficient for congressional action at its inception and for FDA to take the rare step of imposing restrictive controls on access to the drug—demand equally serious consideration of the appropriate bioequivalence requirements to ensure that

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[94] *Id.*
[95] *Id.*
[96] *Id.*
[97] 21 C.F.R. § 320.1(e).
[98] 21 C.F.R. § 320.22(b).
[99] *Id.* (emphasis added).
[100] 21 U.S.C. § 355(j)(7)(A)(i)(III).

generic sodium oxybate products will produce the same results in patients as Xyrem. At the present time, FDA should require *in vivo* bioequivalence studies for generic products that differ from Xyrem in manufacturing process, pH, excipients, impurities, degradants, or contaminants.

a. FDA Should Require *In Vivo* Bioequivalence Studies for Generic Sodium Oxybate Products with Formulations Different From Xyrem

As discussed above, for ANDAs referencing Xyrem, the law mandates that FDA publish whether *in vivo*, *in vitro*, or both such bioequivalence tests are required.[101] Jazz is unaware of data sufficient to support an *in vitro*-only showing of bioequivalence for generic sodium oxybate products that are not the same as Xyrem with respect to manufacturing process, pH, excipients, impurities, degradants, and contaminants.[102] In fact, as discussed further below, available evidence suggests that formulation differences may alter *in vivo* absorption of generic sodium oxybate formulations.

Consequently, in the absence of the data required under FDA's regulations to rule out absorption effects of these types of formulation differences and thereby permit waiver of *in vivo* bioequivalence studies, Jazz requests in this petition that FDA require *in vivo* bioequivalence testing for generic sodium oxybate products that do not replicate Xyrem's manufacturing process or pH, or have qualitatively or quantitatively different excipient, impurity, degradant or contaminant profiles.

b. To Only Require *In Vitro* Bioequivalence Studies for Generic Sodium Oxybate Formulations, FDA Must Either Require No Difference in Formulation from Xyrem, or Determine that No Change in the Generic Formulation "May Significantly Affect Absorption"

To the extent that FDA determines to require only *in vitro* bioequivalence testing for generic sodium oxybate products that differ from Xyrem in manufacturing process, pH, excipients, impurities, degradants, and/or contaminants, then waiver of *in vivo* bioequivalence testing would require "data"[103] showing that the ANDA product:

> [c]ontains no inactive ingredient or other change in formulation from the [RLD] . . . that may significantly affect absorption of the active drug ingredient or active moiety for products [like SXB] that are systemically absorbed...[104]

Application of this standard to a proposed generic sodium oxybate product would necessitate several things. First, a detailed understanding of the Xyrem formulation would be needed. Second, an equally detailed comparison of the proposed generic formulation to Xyrem would be

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[101] *Id.*

[102] For generic sodium oxybate products that replicate the Xyrem manufacturing process and pH and have the same excipients, impurities, degradants, and contaminants in the same quantities, Jazz believes that FDA would be on stronger ground not to require *in vivo*, but instead only require *in vitro*, evidence of bioequivalence.

[103] 21 C.F.R. § 320.22(b).

[104] 21 C.F.R. § 320.22(b)(3)(iii).

required in order to characterize all changes in the generic formulation as compared to Xyrem. Third, FDA would have to, based on data, assess whether any such "inactive ingredient or other change in formulation . . . may" affect absorption of the generic sodium oxybate product in patients. Lastly, FDA would need to establish valid methods to determine whether any such possible effects on absorption may be "significant."

Again, Jazz is unaware of any data sufficient to rule out potentially significant absorption differences associated with differences in sodium oxybate product formulations. In fact, to the contrary, as discussed further below, available evidence indicates that there are several reasons why generic sodium oxybate products that differ from Xyrem in manufacturing process, pH, excipients, impurities, degradants, or contaminants may have different absorption characteristics than Xyrem. There is no evidence that a generic SXB product with different absorption characteristics will be equivalent to Xyrem in safety or efficacy.

c. The Xyrem Formulation Results From a Unique, Proven, Proprietary Manufacturing Process

The Xyrem manufacturing process was established through empirical observation and produces a formulation of SXB that has been proven through extensive clinical trials and more than 35,000 patient-years of exposure to be stable, safe, and effective.[105]

Xyrem's proprietary manufacturing process results in an aqueous sodium oxybate solution consisting of a monocarboxylic acid, a dicarboxylic acid, and a sodium counterion and is well defined with respect to pH, excipients, impurities, degradation products and contaminants. Xyrem's manufacturing begins with a grade of GBL that is not commercially available, but rather specially produced for Xyrem. As a result of Xyrem's formulation, the uncontrolled degradation of SXB into GBL and other products is limited, and Xyrem is completely stable over the entirety of the 60-month shelf life of the product.

Xyrem's formulation benefits from rigorous quality control standards that include tight specifications for the overall purity of the GBL starting material and the product's final pH. The final product of Jazz's manufacturing process quickly reaches a thermodynamically stable chemical equilibrium between GBL and SXB that provides for highly predictable and reproducible GBL levels throughout the life of the product. As such, Jazz's Xyrem drug formulation is unique in its chemical stability and demonstrated ability to remain unchanged irrespective of time and temperature, from the time it is bottled throughout the shelf life of the drug product.

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[105] FDA, CENTER FOR DRUG EVALUATION AND RESEARCH, Jazz Core Presentation, Presentation by Diane Guinta, Ph.D., Jazz Pharmaceuticals, Inc.: Efficacy Overview, Joint Meeting of the Arthritis Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee, p. 50 (Aug. 20, 2010). *Exhibit 30.*

5. Formulation Differences May Affect In Vivo Absorption of Generic Sodium Oxybate Products and the Safety and Efficacy of the Drug

a. Differences in Levels of GBL May Affect Absorption

GBL is the manufacturing precursor to the pharmacologically active sodium oxybate moiety. *In vivo*, GBL is directly metabolized to GHB. GBL can be present in the final formulation of a sodium oxybate solution as a manufacturing contaminant and is also produced as the product of a pH dependent degradation reaction.[106]

GBL is more lipophilic than SXB and, following oral administration, is rapidly absorbed into systemic circulation where it is then quickly converted to the pharmacologically active GHB moiety. As a result, onset of motor impairment is faster after ingestion of the pro-drug GBL than when compared to SXB.[107] Given the rapid absorption of GBL across the gut wall and subsequent conversion to GHB, sodium oxybate formulations containing differing amounts of the pro-drug GBL can differ in both plasma levels of GHB and onset of action for the active drug product following oral administration.

Given the importance of Xyrem's excipient profile in controlling undesirable levels of GBL, any departure from this validated process for the production of the ultra-pure Xyrem formulation of SXB has the potential to yield variable levels of the rapidly acting pro-drug GBL. This may occur at the outset as a result of a generic sodium oxybate product's different manufacturing process, over time due to differences in the rate of degradation between formulations, or some combination of both.

Further, the impact of even small differences in GBL levels between sodium oxybate products on onset of clinical action (i.e., profound sedation) remains unknown. Given the rapid onset of drug action and safety concerns regarding the absence of patient awareness of imminent sleep onset in some instances, to ensure product safety the contribution of even small differences in GBL levels between products needs to be characterized with respect to impact on sleep onset.

However, ANDA applicants, without knowledge of the Xyrem empirical manufacturing experience or proprietary processes, are unlikely to replicate Xyrem's manufacturing process, pH, excipients, impurities, degradants and contaminants. Thus, to the extent ANDA applicants referencing Xyrem cannot demonstrate that their manufacturing process, pH, excipients, impurities, degradants and contaminants are the same as Xyrem's, they should conduct fasted and fed *in vivo* bioequivalence studies to rule out potential PK and PD differences associated with variations in levels of GBL to ensure that a generic SXB product is as safe and effective as Xyrem.

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[106] "Problems with the storage of GHB solutions still exist. GHB degrades into gamma-butyrolactone (GBL) and possibly other degradants in solution depending upon the pH and other factors. Also, the contamination by microorganisms in GHB solutions rapidly surpass acceptable limits, and preservatives can adversely affect the pH and thus, GHB's stability." U.S. Patent No. 7,851,506, col. 2, lines 49-54. *Exhibit 31.*

[107] Goodwin *supra* note 5.

b. Generic Sodium Oxybate Formulation Differences May Affect Active Transport of GHB and Therefore Absorption

The role of drug transporters as key players in the processes of drug absorption, distribution, metabolism, and elimination has been well established, and intestinal transporters have the potential to dramatically influence pharmacokinetic parameters, including bioavailability, exposure, clearance, volume of distribution, and half-life, for orally dosed drugs.[108] Recent work indicates drug transporters are critical to the absorption of GHB.[109] Consequently, generic SXB formulations that differ from Xyrem in manufacturing process, pH, excipients, degradants, or contaminants may result in different therapeutic concentrations, i.e., bio*in*equivalence.

Existing mainly as membrane-bound proteins, transporters can either facilitate a drug's access to the cell or limit the access to certain tissues, thereby not only determining the pharmacokinetics of a drug, but also a drug's pharmacodynamic reaction by governing the delivery of the drug to the site of action and also determining the tissue concentration of a drug.[110] As a result of the contribution of transporters to variability in drug concentration and response, unexpected toxicities or drug-drug interactions may occur.[111]

In recognition of the growing body of evidence highlighting the importance of understanding the role of drug transporters in therapeutic and adverse drug responses, the International Transporter Consortium (ITC) was formed in 2007 and consists of scientists from academia, industry, and the FDA.[112] Based on their work, the ITC published a white paper in 2010 intended to help guide clinical studies on the currently recognized most important drug transporter interactions.[113]

As recently as March 2010, FDA has empaneled its Advisory Committee for Pharmaceutical Science and Clinical Pharmacology (ACPS) to discuss how best to incorporate the growing understanding of the important role that transporters play into the regulatory approval process. At the March 17, 2010 ACPS Meeting, FDA's Dr. Lei Zhang, Special Assistant to the Office Director for the Office of Clinical Pharmacology, reported that transporters have been found to

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[108] *See, e.g.,* Shugarts S, Benet LZ. The role of transporters in the pharmacokinetics of orally administered drugs. *Pharm Res.* 2009 Sep;26(9):2039-54. *Exhibit 32.*

[109] Morris ME, Felmlee MA. Overview of the proton-coupled MCT (SLC16A) family of transporters: characterization, function and role in the transport of the drug of abuse gamma-hydroxybutyric acid. *AAPS J.* 2008 Jun;10(2):311-21. *Exhibit 33.*

[110] Zhang L, Huang SM, Lesko LJ. Transporter-mediated drug-drug interactions. *Clin Pharmacol Ther.* 2011 Apr;89(4):481-4. *Exhibit 34.*

[111] FDA, CENTER FOR DRUG EVALUATION AND RESEARCH, Presentation by Lei Zhang, FDA: Transporter-Mediated Drug Interactions, Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting, p. 2 (Mar. 17, 2010).

[112] Huang SM, Zhang L, Giacomini KM. The International Transporter Consortium: a collaborative group of scientists from academia, industry, and the FDA. *Clin Pharmacol Ther.* 2010 Jan;87(1):32-6. *Exhibit 35.*

[113] International Transporter Consortium, Giacomini KM, Huang SM, Tweedie DJ, Benet LZ, Brouwer KL, Chu X, Dahlin A, Evers R, Fischer V, Hillgren KM, Hoffmaster KA, Ishikawa T, Keppler D, Kim RB, Lee CA, Niemi M, Polli JW, Sugiyama Y, Swaan PW, Ware JA, Wright SH, Yee SW, Zamek-Gliszczynski MJ, Zhang L. Membrane transporters in drug development. *Nat Rev Drug Discov.* 2010 Mar;9(3):215-36. Review. *Exhibit 36.*

be very important in determining "a drug's pharmacokinetics through the absorption, distribution, metabolism, as well as excretion process."[114]

In humans, GHB exhibits nonlinear pharmacokinetics related to capacity-limited absorption.[115] GHB undergoes limited renal elimination[116] due to reabsorption mechanisms that have recently been shown to be mediated by Monocarboxylic Acid Transporters (MCT).[117] MCTs are transport proteins that determine the absorption, renal clearance, and distribution of GHB throughout the body, including its distribution to the brain, the site of action.[118] Recent work has examined the MCT-mediated intestinal absorption of GHB and shown it to occur in a concentration- and proton gradient-dependent manner.[119] Studies have further demonstrated that GHB transport occurs via a carrier-mediated process in the intestine facilitated by MCTs, which have been demonstrated to be present along the entire length of the human intestine.[120] Based on the fact that at physiologic pH more than 99% of GHB is ionized and cannot diffuse across cellular membranes, the MCT-mediated intestinal absorption of GHB can be assumed to be critical to the onset of its pharmacological activity.

Understanding transporters and their interaction with both drug products and excipients can provide a mechanistic approach to explain variability in pharmacokinetics, pharmacodynamics, and safety in clinical trials.[121] Recent work on drug transporters has triggered a reevaluation of traditional assumptions that tended to discount the possibility of absorption effects resulting from formulation differences in pharmaceutically equivalent formulations. For example, the effects of transporter-mediated absorption of a drug on traditional assumptions made about bioequivalence are a key factor in the recent development of the Biopharmaceutics Drug Disposition Classification System (BDDCS) classification scheme.[122] As a result, the BDDCS seeks to

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[114] FDA, CENTER FOR DRUG EVALUATION AND RESEARCH, Meeting Transcript, Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting, p. 195 (Mar. 17, 2010) [hereinafter *PSCP Meeting*].

[115] Palatini P, Tedeschi L, Frison G, Padrini R, Zordan R, Orlando R, Gallimberti L, Gessa GL, Ferrara SD. Dose-dependent absorption and elimination of gamma-hydroxybutyric acid in healthy volunteers. *Eur J Clin Pharmacol.* 1993;45(4):353-6. *Exhibit 37.*

[116] Brenneisen R, Elsohly MA, Murphy TP, Passarelli J, Russmann S, Salamone SJ, Watson DE. Pharmacokinetics and excretion of gamma-hydroxybutyrate (GHB) in healthy subjects. *J Anal Toxicol.* 2004 Nov-Dec;28(8):625-30. *Exhibit 38.*

[117] Morse BL, Felmlee MA, Morris ME. γ- Hydroxybutyrate blood/plasma partitioning: effect of physiologic pH on transport by monocarboxylate transporters. *Drug Metab Dispos.* 2012 Jan;40(1):64-9. *Exhibit 39.*

[118] Wang Q, Morris ME. The role of monocarboxylate transporter 2 and 4 in the transport of gamma-hydroxybutyric acid in mammalian cells. *Drug Metab Dispos.* 2007 Aug;35(8):1393-9. *Exhibit 40.*

[119] Lam WK, Felmlee MA, Morris ME. Monocarboxylate transporter-mediated transport of gamma-hydroxybutyric acid in human intestinal Caco-2 cells. *Drug Metab and Dispos.* 2010 Mar;38(3):441-7. *Exhibit 41.* The study "represents the first investigation of the role of MCTs in the intestinal absorption of GHB. We have demonstrated that GHB and D-lactate are taken up into Caco-2 cells in a concentration- and proton gradient-dependent manner, indicating the involvement of MCTs. Their uptake and directional flux were also inhibited by the known MCT inhibitor CHC, as well as the MCT substrates D-lactate and GHB." *Id.*

[120] Morris *supra* note 109.

[121] *PSCP Meeting* at 218.

[122] Benet LZ. Predicting drug disposition via application of a Biopharmaceutics Drug Disposition Classification System. *Basic Clin Pharmacol Toxicol.* 2010 Mar;106(3):162-7. *Exhibit 42.*

incorporate the effects that drug transporters exert on oral drug pharmacokinetic parameters for bioequivalence predictions.[123]

Furthermore, low affinity and high capacity uptake transporters such as MCT1 have been recognized for the role that they play in the uptake of high oral dose hydrophilic and polar drugs.[124] In the case of new drug applications, FDA has previously recommended the evaluation of transporter-based drug interactions for multidrug resistance P-glycoprotein (MDR1 P-gp) and has said that the evaluation of other transporter systems may be recommended on a case-by-case basis.[125]

These findings are relevant to sodium oxybate oral solution products and particularly important in light of the serious risks associated with GHB. In light of what is now known about the importance of MCT-mediated transport of GHB, it is clear that any differences in formulation between a generic sodium oxybate product and Xyrem with the potential to result in transporter-based drug or excipient interactions should be evaluated in order to ensure that the differences do not result in the generic product having an altered pharmacokinetic profile compared to Xyrem. Due to the nonlinear absorption profile and rapid metabolism and excretion of GHB, the purity and stability of any generic sodium oxybate product should be held to the same or higher tolerances as Xyrem for any consideration of bioequivalence. Based on the rapid metabolism of GHB, and research demonstrating that the uptake of GHB can be competitively inhibited in the presence of other MCT substrates,[126] any change in the rate of MCT-mediated absorption caused by differences in manufacturing processes, pH, excipients, degradants, or contaminants could result in differences in plasma concentrations and altered biological activity.

Given these circumstances, different sodium oxybate formulations may exhibit different rates and extents of absorption *in vivo*. Consequently, absent an *in vivo* demonstration of bioequivalence, such a generic formulation of GHB could potentially be approved as bioequivalent to Xyrem even though it exhibits different absorption from Xyrem, and thus may fail to achieve the safety and efficacy achieved by Xyrem.

c. Generic Sodium Oxybate Formulation Differences Could Alter the Food Effect Seen With Xyrem

As stated in the Xyrem label, there is a food effect associated with sodium oxybate administration.[127] SXB is rapidly but incompletely absorbed after oral administration, and absorption is delayed and decreased by a high fat meal.[128]

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[123] Broccatelli F, Cruciani G, Benet LZ, Oprea TI. BDDCS Class Prediction for New Molecular Entities. *Mol Pharm.* 2012 Mar 5;9(3):570-80. *Exhibit 43.*

[124] Varma MV, Ambler CM, Ullah M, Rotter CJ, Sun H, Litchfield J, Fenner KS, El-Kattan AF. Targeting intestinal transporters for optimizing oral drug absorption. *Curr Drug Metab.* 2010 Nov;11(9):730-42. *Exhibit 44.*

[125] Zhang L, Zhang YD, Strong JM, Reynolds KS, Huang SM. A regulatory viewpoint on transporter-based drug interactions. *Xenobiotica.* 2008 Jul;38(7-8):709-24. *Exhibit 45.*

[126] Cui D, Morris ME. The drug of abuse gamma-hydroxybutyrate is a substrate for sodium-coupled monocarboxylate transporter (SMCT) 1 (SLC5A8): characterization of SMCT-mediated uptake and inhibition. *Drug Metab Dispos.* 2009 Jul;37(7):1404-10. *Exhibit 46.*

[127] Xyrem® Package Insert, p. 11 (Nov. 18, 2005).

Food has a significant effect on the oral bioavailability of Xyrem. In clinical studies comparing dosing of Xyrem in patients after either an overnight fast or a high-fat meal, it was found that food significantly altered the bioavailability of SXB by decreasing mean peak plasma concentration by a mean of 58%, increasing median time-to-peak concentration, and decreasing the area under the plasma concentration-time curve by a mean of 37%. While drug absorption was significantly altered, food was reported to have no effect on the elimination and urinary excretion of unchanged drug.[129]

While the effect of food on the intestinal uptake of drugs that are poorly permeable continues to be researched, evidence suggests that after a high-fat meal the intestinal uptake of these agents is significantly decreased due to the inhibition of anionic transporters, such as the MCTs that play an important role in the absorption of GHB.[130] Due to the variability of this effect on poorly metabolized and poorly permeable drugs, changes in absorption continue to be difficult to model and are an area of active research.

Given the potential (1) for food to affect the onset of action of GHB, (2) the known role of active transporters in the absorption of the polar and highly ionized GHB moiety and not the lipophilic pro-drug GBL, and (3) the potential for excipients and pH to alter the active transport of GHB from the gut into systemic circulation, *in vivo* bioequivalence testing of any generic sodium oxybate formulation that differs from Xyrem should be required under both fasted and fed conditions to ensure that a generic SXB product is as safe and effective as Xyrem.

d. The Serious Risks Associated with Sodium Oxybate Justify a Conservative Approach to Identifying Formulation Differences that "May Significantly Affect" Absorption

Xyrem is one of the rare drug products where FDA has required a REMS with ETASU because, among other things, there are serious risks to the patient even when SXB is taken as prescribed.[131] This alone is reason enough for FDA to be careful and conservative with respect to any determination that *in vivo* bioequivalence testing can be waived for a sodium oxybate formulation that differs from Xyrem.

The risk of serious adverse events is magnified when patients also take certain other agents in addition to SXB, particularly in the case of co-administration with CNS depressants[132] or alcohol.[133] Under such multi-factorial pharmacologic circumstances, generic sodium oxybate formulations that differ from Xyrem may exhibit further absorption differences with clinical

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[128] Borgen *supra* note 17.
[129] *Id.*
[130] Custodio JM, Wu CY, Benet LZ. Predicting drug disposition, absorption/elimination/transporter interplay and the role of food on drug absorption. *Adv Drug Deliv Rev.* 2008 March 17; 60(6): 717-33. *Exhibit 47.*
[131] Xyrem® Package Insert, p. 1 (Nov. 18, 2005).
[132] Atkins BE, Miranda E, Lacy JM, Logan BK. A multi-drug intoxication fatality involving Xyrem (GHB). *J Forensic Sci.* 2009 Mar;54(2):495-6. *Exhibit 48.*
[133] Thai D, Dyer JE, Benowitz NL, Haller CA. Gamma-hydroxybutyrate and ethanol effects and interactions in humans. *J Clin Psychopharmacol.* 2006 Oct;26(5):524-9. *Exhibit 49.*

significance. To rule out (as FDA's *in vivo* bioequivalence waiver regulation and good public health science stewardship require) the possibility that differing generic sodium oxybate formulations "may significantly affect" absorption in these circumstances where adverse event risks are elevated would require a robust level of evidence that, to Jazz's knowledge, does not exist.

6. Multiple Generics With Multiple Formulation Differences Would Potentially Multiply the Risk to Patients

Xyrem also illustrates the logic of the law's mandate that bioequivalence requirements be promulgated so that uniformity among generic versions of a given reference listed drug is ensured. For Xyrem this is particularly important. Without the legally mandated uniformity in bioequivalence requirements for generic sodium oxybate products, FDA might approve multiple such products with various different formulations, and multiple, unknown absorption differences among the formulations.

Patients and practitioners familiar with how Xyrem works will expect generic "copies" to behave in the same way. This includes a predictable onset of action and side effect profile. Many of the side effects associated with Xyrem use are uptake dependent, as is the interval from dosing to onset of action. Patients should not be exposed to multiple sodium oxybate formulations that each could alter those drug effects.

As just discussed, there are, at a minimum, several known reasons why a generic formulation that differs from Xyrem might alter absorption of drug active ingredient vis-à-vis Xyrem. Thus approval of a single generic sodium oxybate product as equivalent to Xyrem despite the fact that it has a different formulation carries risk of differential absorption. And under its regulations, to dispense with *in vivo* bioequivalence testing FDA has the burden to determine whether sufficient data exist to rule out the possibility that formulation differences "may significantly affect absorption."[134]

For FDA to permit multiple differing generic sodium oxybate formulations would magnify this risk, as well as FDA's workload. Rather than simply promulgate, as the law mandates, uniform bioequivalence requirements for generic sodium oxybate products, FDA would have to assess each individual formulation difference in each generic drug product, and rule out the possibility that such differences, individually or in combination, "may significantly affect absorption."[135] Patients and practitioners in a multisource environment, where the particular product with which a prescription is filled may vary monthly, must be assured that there will be no significant absorption differences across all such products, including new ones as they receive approval.

* * *

[134] 21 C.F.R. §§ 320.22(b), (b)(3)(iii).
[135] *Id.*

In sum, while the Xyrem manufacturing process has for years consistently produced the same Xyrem product, it has yet to be established that generic formulations which differ from Xyrem in manufacturing process, pH, excipients, contaminants, impurities, or degradants will possess the same absorption and onset of action characteristics as Xyrem; available evidence suggests they would not. Accordingly, due to the potential for toxicity endpoints that include coma or even death for both GBL and GHB, in order to ensure patient safety any ANDA product whose manufacturing process, pH, excipients, contaminants, impurities, or degradants differ from Xyrem's should be required to submit *in vivo* bioequivalence data and demonstrate an equivalent rate of absorption in both fed and fasted conditions, and an equivalent onset of drug action, such that the safety profile and time to sleep onset observed with Xyrem will not be altered.

III. CONCLUSION

For all of the reasons set forth above, Jazz respectfully requests that FDA take the actions requested in this petition.

IV. ENVIRONMENTAL IMPACT

This petition is categorically exempt from the requirement for an environmental assessment or environmental impact statement under 21 C.F.R. §§ 25.30 and 25.31.

V. ECONOMIC IMPACT

Information on the economic impact of this petition will be provided upon request.

VI. CERTIFICATION

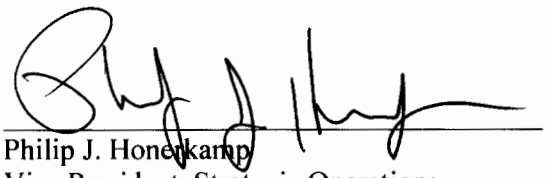
Pursuant to 21 C.F.R. § 10.30(b), the undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Pursuant to 21 U.S.C. § 355(q)(1)(H):

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: April 10, 2012 (information about therapeutic

equivalence evaluations), March 12, 2012 (information about bioequivalence requirements), February 1, 2012 (information in scientific publication), October 14, 2010 (information that an ANDA had been submitted), April 1, 2010 (information in scientific publication), August 1, 2009 (information in scientific publication), July 1, 2008 (information in scientific publication), September 1, 2007 (information in scientific publication), November 18, 2005 (FDA approval and labeling for new indication), July 17, 2002 (initial FDA approval and labeling). If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Jazz Pharmaceuticals, Inc. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Sincerely,



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