Jazz Pharmaceuticals®

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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 the Commissioner of Food and Drugs take the actions described below. Jazz is the NDA-holder of XYREM® (sodium oxybate) oral solution (Xyrem), which is indicated for the treatment of cataplexy and excessive daytime sleepiness in patients with narcolepsy. This petition addresses abbreviated new drug applications (ANDAs) referencing Xyrem, including an ANDA submitted by Roxane Laboratories, Inc. (Roxane) on July 8, 2010.

I. ACTIONS REQUESTED

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

1. Rescind the acceptance of any previously-accepted ANDA referencing Xyrem, including Roxane's ANDA, that did not contain, at the time it was accepted for review, a proposed risk management system, as such an ANDA would not have demonstrated, as required by law, that the proposed ANDA drug product would have the same labeling and the same conditions of use as Xyrem.

2. Not accept for review any ANDA referencing Xyrem that does not contain, at the time of its submission, a proposed risk management system sufficient to demonstrate that the proposed ANDA drug product would have the same labeling and the same conditions of use as Xyrem.

3. If the sponsor (including Roxane) of an ANDA referencing Xyrem that did not contain, at the time it was accepted for review, a proposed risk management system later submits, or resubmits, an ANDA referencing Xyrem that contains a proposed risk management system sufficient to demonstrate that the proposed ANDA drug product would have the same labeling and the same conditions of use as Xyrem, not approve such ANDA for a

3180 Porter Drive, Palo Alto, CA 94304
p 650.496.3777 f 650.496.3781

1818 Market Street, Suite 2350, Philadelphia, PA 19103
p 215.832.3750 f 215.832.3789

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2012-5780

period of up to thirty months beginning on the date Jazz receives notice of any Paragraph IV certifications contained in such new ANDA, in accordance with 21 U.S.C. 355(j)(5)(B)(iii), to the extent that Jazz avails itself of its right to initiate a patent infringement action based on such notice.

II. STATEMENT OF GROUNDS

A. Factual Background

1. Xyrem is an important drug with a unique risk profile.

Xyrem is the sodium salt of gamma-hydroxybutyric acid (GHB), and it is indicated for the treatment of cataplexy and excessive daytime sleepiness (EDS) in patients with narcolepsy[1]—a rare and debilitating sleep disorder.[2] First approved by the FDA in 2002,[3] Xyrem is the only drug considered by the American Academy of Sleep Medicine to be a standard of care for the treatment of both narcolepsy symptoms for which it is indicated.[4]

While beneficial as an FDA-approved, and carefully controlled, drug product, GHB also has a notorious history, having been abused recreationally (as a "club drug") and, more nefariously, as a so-called "date-rape" drug. In 1990, based on more than 30 reports of GHB-linked illness,[5] the FDA declared the drug—which had previously been available on store shelves as a dietary supplement—unsafe and illegal, except in the carefully controlled environment of FDA-regulated clinical studies.[6]

By 1990, preliminary research had indicated that GHB had therapeutic promise in treating patients with narcolepsy.[7] In light of this research, and because existing treatment options for such patients were limited, the FDA approached Orphan Medical, Inc. (Orphan), in the mid-1990s, to conduct additional research into the therapeutic use of GHB.[8]

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

[2] Beusterien KM, Rogers AE, Walsleben JA, Emsellem HA, Reblando JA, Wang L, Goswami M, Steinwald B. Health-related quality of life effects of modafinil for treatment of narcolepsy. *Sleep.* 1999 Sep 15;22(6):757-65. *Exhibit 1.*

[3] 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*]. *Exhibit 2.*

[4] 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 3.*

[5] GHB intoxication is a significant cause of morbidity and mortality in those abusing the drug for recreational purposes. *See* 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. Review. *Exhibit 4.*

[6] Nordenberg T. The death of the party: All the rave, GHB's hazards go unheeded. *FDA Consum.* 2000 Mar-Apr;34(2):14-16, 18-19. *Exhibit 5.*

[7] *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), *available at* http://www.fda.gov/ohrms/dockets/ac/01/slides/3754s1.htm. *Exhibit 6.*

[8] *Id.*

Around the same time, reports began to surface of women dying or being sexually assaulted after illegal GHB was slipped into their drinks.[9] In 2000, alarmed by these reports, Congress made a rare departure from its traditional stance of leaving drug scheduling to the executive branch, and passed the Hillory J. Farias and Samantha Reid Date-Rape Drug Prohibition Act, which bifurcated controlled substance scheduling for GHB.[10] The law made GHB a Schedule I drug,[11] but also provided that an FDA-approved drug containing GHB could be listed as a Schedule III drug.[12] At the time of the bill's passage, the FDA had not approved Xyrem.

Two years later, following successful clinical trials, the FDA approved Xyrem for the treatment of cataplexy in patients with narcolepsy.[13] And, in 2005, three years after its initial approval, the FDA approved Xyrem for the treatment of EDS in patients with narcolepsy.[14]

Today, Xyrem remains the only FDA-approved treatment for cataplexy, one of the most disabling features of narcolepsy,[15] and it enables patients suffering from this symptom to resume a more normal life.[16] Patients taking Xyrem also get relief from EDS, a ubiquitous and, typically, severe feature of narcolepsy that has been associated with an array of negative psychosocial and emotional effects, such as difficulty with interpersonal relationships and trouble maintaining employment.[17]

2. **Xyrem's unique risks led the FDA to restrict its use.**

Recognizing that Xyrem presented unique and substantial risks, the FDA approved the drug

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[9] Nicholson KL, Balster RL. GHB: a new and novel drug of abuse. *Drug Alcohol Depend.* 2001 Jun 1;63(1):1-22. Review. *Exhibit 7*; Schwartz RH, Milteer R, LeBeau MA. Drug-facilitated sexual assault ('date rape'). *South Med J.* 2000 Jun;93(6):558-61. Review. *Exhibit 8.*

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

[11] Schedule I controlled substances have a high potential for abuse, have no currently accepted medical use in treatment in the U.S., and there is a lack of accepted safety for their use under medical supervision. *See* 21 U.S.C. 812(b)(1).

[12] Hillory J. Farias and Samantha Reid Date-Rape Drug Prohibition Act of 2000, Pub. L. No. 106-172, 114 Stat. 7, sec. 3(a)(1)(B) (2000); *see also* Letter from David Satcher, Asst. Secretary for Health and Surgeon General, HHS to Donnie R. Marshall, Deputy Administrator, DEA (May 19, 1999), *available at* http://www.deadiversion.usdoj.gov/fed_regs/rules/2000/fr0313.htm. *Exhibit 9.*

[13] *See Xyrem Approval Letter #1.*

[14] *See* 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*]. *Exhibit 10.*

[15] *See* JODY COREY-BLOOM & RONALD DAVID, CLINICAL ADULT NEUROLOGY 180 (2008). *Exhibit 11.*

[16] *See* 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 12.*

[17] *See* Broughton WA, Broughton RJ. Psychosocial Impact of Narcolepsy, *Sleep.* 1994 Dec;17(8Suppl):S45-9. Review. *Exhibit 13*; Roger Broughton & Quais Ghana, *The Impact of Compound Narcolepsy on the Life of the Patient, in* NARCOLEPSY 201, 201-20 (Christian Guilleminault et al. eds., 1976) ("[Narcolepsy] frequently leads to very disturbing visual problems, memory difficulties, an extremely bad driving record, recurrent household and smoking accidents, poor productivity, blocking of promotion, decreased hearing capacity and even job dismissal, personality changes including a striking tendency to depression even to suicidal levels, hallucinations and paranoia, difficulties and embarrassment in both education and recreation, loss of libido and (for males) impotence, miscellaneous disturbance of balance, bizarre dysesthesias, terrifying dreams, headaches, and the danger of loss of life through accident or drowning."). *Exhibit 14.*

under 21 C.F.R. 314, Subpart H,[18] pursuant to which the Agency can require extraordinary restrictions on a drug product's use.[19] Specifically, where the FDA "concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted," the FDA can require "such postmarketing restrictions as are needed to assure safe use of the drug product."[20]

In the case of Xyrem, the FDA required specific restrictions on distribution and use, including:

1) Implementation of a restricted distribution program for Xyrem.

2) Implementation of a program to educate physicians and patients about the risks and benefits of Xyrem, including critical information necessary for the safe use and handling of the drug.

3) Filling of the initial prescription only after the prescriber and patient have received and read the educational materials.

4) Maintenance of a registry of all patients and a record of all prescribers.[21]

In approving Xyrem, the FDA also determined that the drug "poses a serious and significant public health concern requiring distribution of a Medication Guide. . . . [which] is necessary to help prevent serious adverse events due to Xyrem® pursuant to 21 CFR Part 208.1(c)(1)."[22] Consequently, the FDA required Xyrem's sponsor (Jazz's predecessor, Orphan Medical) to ensure that:

- A Medication Guide for Xyrem is available for every patient who is dispensed a prescription for Xyrem.
- The label of each carton container of Xyrem includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom Xyrem is dispensed.
- The label of each container includes a statement about how the Medication Guide is dispensed.[23]

The FDA-mandated controls on Xyrem's distribution and use are effectuated through the Xyrem Success Program®. Known initially as a "Risk Management Program,"[24] the Xyrem Success Program is now a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU).[25] The concept of REMS was created as part of the Food and Drug

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[18] *See* 21 C.F.R. 314.500-314.560.
[19] 21 C.F.R. 314.520 (titled "Approval with restrictions to assure safe use").
[20] 21 C.F.R. 314.520(a).
[21] *Xyrem Approval Letter #1* at 2.
[22] *Id.*
[23] *Id.*
[24] *Id.* at 1-2.
[25] REMS may consist of one or more elements, including medication guides, communication plans, and ETASU. 21 U.S.C. 355-1(f). REMS with ETASU—the most restrictive REMS—are implemented to assure safe use of the drug when an assessment and Medication guide, patient package insert, or communication plan would not be

Administration Amendments Act (FDAAA) of 2007.[26] Among other things, FDAAA addressed previously-approved drug products, like Xyrem, that had in effect, as of the effective date of the Act, restrictions to assure safe use required under 21 C.F.R. § 314.520. Those drug products were, by Congressional decree, "deemed to have in effect an approved risk evaluation and mitigation strategy under section 505-1 of the [FDCA]."[27] Such REMS consist of, *inter alia*, the drug's then-existing restrictions to assure safe use, as well as its Medication Guide, patient package insert, and communication plan—to the extent that such "restrictions" or elements existed.[28] Xyrem, approved by the FDA in 2002, was subject to a number of "restrictions" (now known as "elements") that remained in effect as of FDAAA's effective date. Thus, Xyrem was among the drug products pre-dating FDAAA expressly deemed to have in effect an approved REMS with ETASU.[29] This REMS remains in place[30] and is governed by Section 505-1 of the FDCA.

The classification of the Xyrem Success Program as a REMS did not alter the underlying law requiring any ANDA referencing Xyrem to contain information showing that its proposed labeling and conditions of use—including those incorporated in the Xyrem Success Program—are the same as Xyrem's (as discussed, at length, *infra*). Thus, the Actions Requested in this Petition, which are predicated upon law applicable to all ANDAs, would be compelled regardless of whether Xyrem was subject to a REMS or to one of its regulatory precursors (*e.g.*, a Risk Minimization Action Plan (RiskMAP)).

3. **The Xyrem Success Program.**

The Xyrem Success Program was created to permit Xyrem's approval consistent with the conditions that the FDA placed on the use of Xyrem. Physicians and patients are introduced to Xyrem, and the Xyrem Success Program, through an array of educational materials, which describe the drug, its associated risks, and the complex central distribution system that ensures Xyrem is delivered to and appropriately used by—and only by—the persons for whom it is prescribed. These materials include a Xyrem Medication Guide, as well as (1) a Xyrem Success Program for Physicians informational booklet; (2) a "Dear Prescriber" Letter; (3) a Physician

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sufficient to mitigate the drug's risk. *See* 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. 11 (Sep. 2009), *available at* http://www.fda.gov/downloads/Drugs/ GuidanceComplianceRegulatoryInformation/Guidances/ucm184128.pdf. The ETASU, which are selected "to mitigate...specific serious risk[s] listed in the labeling of the drug," provide additional protection and make approvable, and therefore available, important drugs that would otherwise not be dispensed outside of an investigational setting. 21 U.S.C. 355-1(f)(1)(A).

[26] Food and Drug Administration Amendments Act (FDAAA) of 2007, Pub. L. No. 110-85, 121 Stat. 823 (2007), Title IX, Subtitle A, Section 901 [hereinafter *FDAAA of 2007*].

[27] *FDAAA of 2007*, sec. 909(b)(1).

[28] *FDAAA of 2007*, sec. 909(b)(2). Note that 21 C.F.R. § 314.520 describes "restrictions" to assure safe use, while FDAAA refers to "elements" to assure safe use.

[29] *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).

[30] Jazz also submitted to the FDA, within 180 days of FDAAA's effective date, a proposed REMS for Xyrem, in the new REMS format, as required by FDAAA. *FDAAA of 2007*, sec. 909(b)(3). Jazz's proposal is still pending at the FDA, and is likewise subject to 21 U.S.C. 355-1. *See id.*

Enrollment Form; (4) a Xyrem Titration Schedule; (5) a Xyrem Success Program for Patients informational booklet; (6) a "Dear Patient" letter; (7) a Patient Enrollment and Prescription Form; and (8) a Xyrem Success Program for Patients Video.[31]

The Xyrem Success Program includes several features designed to tightly control, track, and monitor access to Xyrem. For example, prescribers and patients must enroll in the Xyrem Success Program before they can prescribe or use Xyrem.[32] And Xyrem is dispensed only through a central pharmacy, using a central database.[33] This system ensures that only registered prescribers and patients have access to Xyrem; and it allows the pharmacy to track product shipment and delivery, and to monitor usage and refill patterns to identify potential misuse, abuse, or diversion. These protections remain in place throughout the course of Xyrem treatment, with pharmacy staff regularly communicating with patients to discuss and convey important information about the drug and its safe use.

4. **Elements of the Xyrem Success Program are claimed by patents, which are listed in the *Orange Book*.**

Several innovative elements of the Xyrem Success Program received U.S. patents (the "Xyrem Success Program-related patents").[34] These patents claim methods of, *inter alia*, safely treating patients with sodium oxybate while avoiding unwanted abuse, misuse, and diversion associated with the drug, including, but not limited to: using a central pharmacy and a central computer system and database to control distribution and track prescriptions; registering physicians and patients; confirming with patients that educational materials have been provided prior to shipping Xyrem; and monitoring for abuse, misuse, and diversion. The Xyrem Success Program-related patents are listed in the FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* publication (the "Orange Book").

5. **Roxane has submitted an ANDA seeking approval to market a generic version of Xyrem.[35]**

On July 8, 2010, Roxane submitted to the FDA an ANDA seeking approval to market a generic

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[31] *See* Xyrem FDA Approved Labeling Text, Xyrem Risk Management Program, pp. 1-4 (Nov.18, 2005), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2005/021196s005lbl.pdf; *see also* XYREM Success Program® for Physicians, *available at* http://www.xyrem.com/healthcare-professionals/success-program. *Exhibit 15.*

[32] *See* Xyrem FDA Approved Labeling Text, Xyrem Risk Management Program, pp. 1-4 (Nov. 18, 2005), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2005/021196s005lbl.pdf.

[33] *See id.* at 3.

[34] The phrase "Xyrem Success Program-related patents," as used in this Petition, refers to U.S. Patent Nos. 7,668,730 (filed Feb. 23, 2010) *Exhibit 16*; 7,765,106 (filed Jul. 27, 2010) *Exhibit 17*; 7,765,107 (filed Jul. 27, 2010) *Exhibit 18*; and 7,895,059 (filed Feb. 22, 2011). *Exhibit 19.*

[35] All information in this Citizen Petition regarding Roxane's ANDA is based on publicly available material, including material that Roxane has placed, or permitted to be placed, in the public domain in related Hatch-Waxman litigation. *See generally Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*, No. 10-6108 (D.N.J. filed Nov. 11, 2010).

version of Xyrem.[36] On October 14, 2010, Roxane notified Jazz that the FDA had accepted Roxane's ANDA for review, and that the ANDA contained a paragraph IV certification[37] with respect to all patents listed for Xyrem in the Orange Book, including the Xyrem Success Program-related patents.[38] In its paragraph IV notice, Roxane asserted that, although its sodium oxybate product "will be distributed and controlled through a central pharmacy using computer databases and computer aided management protocols substantially the same as those used in connection with the distribution and control of [Xyrem]," the product would not infringe on the Xyrem Success Program-related patents.[39] Roxane's paragraph IV notice led to litigation between the parties, which is currently ongoing.[40]

Although Roxane's October 2010 paragraph IV notice contained assertions regarding Roxane's anticipated method of distributing its sodium oxybate product, it appears that Roxane's ANDA did not, at the time it was submitted, include a proposed risk management system.[41] It also appears that Roxane did not submit any materials relating to its proposed sodium oxybate risk management system until April 2011—over ten months after its initial ANDA submission.[42] And, even then, Roxane submitted only a six-page document,[43] which, according to Roxane, merely "outlined" the "basic elements" of the risk management system that Roxane "was planning on proposing to the FDA."[44] In other words, this April 2011 submission was not a

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[36] *See* FDA, Paragraph IV Patent Certifications, *available at* http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm047676.htm ("The PDF contains the...date on which the first substantially complete generic drug application was submitted to the Agency..."). The PDF regarding the generic Xyrem product is also publicly available. FDA, Paragraph IV Patent Certifications (PDF), *available at* http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM293268.pdf.

[37] A paragraph IV certification claims that the patent in question "is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted." 21 U.S.C. 355(j)(2)(A)(vii)(IV).

[38] Letter from Randall S. Wilson, Vice President, Scientific, Medical and Regulatory Affairs, Roxane Laboratories, Inc. to Jazz Pharmaceuticals, *re: Patent Notice Pursuant to 505(b)(3)(B) [21 U.S.C. § 355(b)(3)(B)]*, pp. 1-11 (Oct. 14, 2010). *Exhibit 20.*

[39] *Id.* at 2.

[40] *See generally Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*, No. 10-6108 (D.N.J. filed Nov. 11, 2010). Following the initiation of this litigation, Jazz listed in the Orange Book two additional patents relating to Xyrem: U.S. Patent Nos. 7,851,506 (filed Dec. 14, 2010) and 7,895,059 (filed Feb. 22, 2010), the latter of which is a Xyrem Success Program-related patent. *Exhibit 21.* Roxane subsequently made paragraph IV certifications with respect to these patents and provided notice to Jazz of such certifications no earlier than January 10, 2011 (for the '506 Patent) and March 22, 2011 (for the '059 Patent). Letter from Randall S. Wilson, Vice President, Scientific, Medical and Regulatory Affairs, Roxane Laboratories, Inc. to Jazz Pharmaceuticals, *re: Patent Notice Pursuant to § 505(j)(2)(B)(ii) [21 USC § 355(j)(2)(B)(ii)]*, pp. 1-7 (Mar. 22, 2011). *Exhibit 22*; Letter from Randall S. Wilson, Vice President, Scientific, Medical and Regulatory Affairs, Roxane Laboratories, Inc. to Jazz Pharmaceuticals, *re: Patent Notice Pursuant to § 505(j)(2)(B)(ii) [21 USC § 355(j)(2)(B)(ii)]*, pp. 1-3 (Jan. 10, 2011). *Exhibit 23.*

[41] Letter from Theodora McCormick, Sills Cummis & Gross, PC to the Honorable Cathy L. Waldor, U.S.M.J., *re: Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*, No. 10-6108, p. 3, n.1 (Jan. 6, 2012) [hereinafter *Roxane's Jan. 6, 2012 Letter*] ("Information regarding a distribution method such as Roxane's REMS is not contained in the original ANDA filing."). *Exhibit 24.*

[42] Letter from Charles M. Lizza, Saul Ewing, LLP to the Honorable Cathy L. Waldor, U.S.M.J., *re: Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*, No. 10-6108, p. 2 (Jan. 19, 2012) [hereinafter *Jazz's Jan. 19, 2012 Letter*]. *Exhibit 25.*

[43] *Id.*

[44] *Roxane's Jan. 6, 2012 Letter* at 2.

complete proposal; it was merely a high-level sketch of what Roxane's risk management system[45] proposal *might* look like if and when Roxane ultimately submitted it in the future.

It further appears that it was not until October 19, 2011, *more than a year* after Roxane initially submitted its ANDA to the FDA, that Roxane, for the first time, submitted anything that could have (even in theory) constituted a substantially complete proposal for a risk management system—a 500-page document providing containing details of such a system.[46] Roxane has asserted that this 500-page document did not include any new information not contained in its earlier 6-page filing, but rather "simply flesh[ed] out the basic elements set forth in" that 6-page document.[47] But Roxane also appears to concede that, until this 500-page document was submitted, at least the following central features of its proposed distribution program had not been revealed to the FDA: (1) identification of the "specific pharmaceutical distributor that will be responsible for carrying out the tasks," (2) "sample patient and doctor forms that will be used to effectuate the elements" of the risk management system; and (3) "a mock-up of the website that Roxane will use to communicate with physicians, pharmacists, and patients."[48]

B. ARGUMENT

This Citizen Petition addresses a narrow issue: whether ANDAs referencing Xyrem, *like all other ANDAs*, must contain information sufficient to demonstrate that the proposed ANDA drug product would have the same labeling and conditions of use as the reference listed drug (here, Xyrem), in order to be accepted for FDA review. Specifically at issue is whether ANDAs referencing Xyrem must contain such information regarding those aspects of the Xyrem Success Program that constitute labeling and/or conditions of use.

It is Jazz's position that the law does *not* treat Xyrem differently than all other drugs. Thus, ANDAs referencing Xyrem must, in order to be acceptable for review, contain information demonstrating that the proposed ANDA drug product would have the same labeling and conditions of use as Xyrem—including those aspects of Xyrem's labeling and conditions of use that are incorporated within the Xyrem Success Program.

Roxane's own public statements suggest that its ANDA did not contain such information at the time it was submitted, which would mean that Roxane's ANDA was improperly accepted for review. If Roxane's ANDA was, in fact, incomplete when filed, then the acceptance of

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[45] In its correspondence with the court, Roxane variously referred to its risk management system as both a "RiskMAP" and a "REMS." *Roxane's Jan. 6, 2012 Letter passim.* Roxane's ultimate position seems to be that Roxane's risk management system is in fact a REMS, as Roxane relies on this position both to deny any duty to have included a REMS in its original ANDA filing and to claim that the Xyrem Success Program-related patents should not be listed in the Orange Book. *Id.* at 3, n. 1. As discussed *infra*, however, the law and the FDA's regulations required Roxane's ANDA, at the time of its filing, to contain the same labeling and conditions of use as Xyrem regardless of whether those required elements were part of a RiskMAP or REMS.

[46] Letter from Charles M. Lizza, Saul Ewing, LLP to the Honorable Cathy L. Waldor, U.S.M.J., *re: Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*, No. 10-6108, p. 2 (Dec. 20, 2011) [hereinafter *Jazz's Dec. 20, 2011 Letter*]. *Exhibit 26.* Because Jazz has not seen Roxane's 500-page submission, Jazz does not know whether it does, in fact, constitute a substantially complete risk management system proposal.

[47] *Roxane's Jan. 6, 2012 Letter* at *2.*

[48] *Id.*

Roxane's ANDA must be rescinded. Such action is required even if Roxane has subsequently supplemented its ANDA with new information that would have rendered the ANDA complete, had such information been included originally (though, public information provides no reason to believe that Roxane has met this standard to date). Moreover, such action is required with respect to any other currently-filed ANDA referencing Xyrem that was similarly incomplete when initially submitted and accepted for review. And, in the future, the FDA should not accept for review any ANDA referencing Xyrem unless and until such ANDA contains a proposed risk management system sufficient to demonstrate that the proposed ANDA drug product would have the same labeling and conditions of use as Xyrem.

1. **The FDA's acceptance of Roxane's ANDA for review was premature and improper.**

    a. **It is inconsistent with the governing law for the FDA to accept for review an ANDA referencing Xyrem—like Roxane's ANDA—that does not contain a substantially complete proposed risk management system, as such an ANDA could not demonstrate that the proposed ANDA drug product would have the same labeling and conditions of use as Xyrem.**

When an ANDA is submitted, the FDA reviews the ANDA to determine whether it may be received—*i.e.*, whether it is "sufficiently complete to permit a substantive review."[49] The FDA may not consider an ANDA to be received if the ANDA "is incomplete because it does not on its face contain information required under [*inter alia*, Section 505(j) and 21 C.F.R. 314.94]."[50] Pursuant to Section 505(j), an ANDA "shall contain . . . information to show," *inter alia*, the following: (1) that "the labeling" proposed for the new drug is the same as the labeling approved for the reference listed drug (RLD);[51] and (2) that the "conditions of use" for the new drug have been previously approved for the RLD.[52]

Certain aspects of the Xyrem Success Program constitute previously approved "labeling" and/or "conditions of use" of Xyrem. Accordingly, the FDA may not receive an ANDA referencing Xyrem unless and until it contains a proposed risk management system with these elements. If, as it appears, Roxane's ANDA did not contain such a system, then accepting that ANDA for review violated the governing statute and regulations. Moreover, it would set a dangerous precedent—and one inconsistent with the FDA's practice in other contexts[53]—if ANDAs could

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[49] 21 C.F.R. 314.101(b)(1).
[50] 21 C.F.R. 314.101(d); d(3).
[51] 21 U.S.C. 355(j)(2)(A)(v).
[52] 21 U.S.C. 355(j)(2)(A)(i).
[53] *See, e.g.*, FDA, NEW DRUG EVALUATION GUIDANCE DOCUMENT: REFUSE TO FILE, (1993) *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080561.pdf (stating FDA's position that the "practice of submitting an incomplete or inadequate application and then 'repairing' it in the course of an extended review period is inherently inefficient and wasteful of agency resources."); *see also, e.g.*, Abbreviated New Drug Application Regulations; Final Rule, 57 Fed. Reg. 17,950 at 17,963, comment 48 (Apr. 28, 1992) (FDA agreeing that "an ANDA application should be complete when submitted and not completed through amendments").

be received for review even though the applicant has failed to develop an aspect of the drug that is necessary for its approval and safe use.

i. *An ANDA referencing Xyrem that does not contain a substantially complete proposed risk management system fails the "same labeling" requirement.*

An ANDA is incomplete, and thus unacceptable for review, if it does not, on its face, contain[54] (1) "specimens of the labeling proposed to be used for such drug,"[55] and (2) "information to show that the labeling proposed for the new drug is the same as the labeling approved for the [RLD] except for changes required because of differences approved under a [suitability petition] or because the new drug and the listed drug are produced or distributed by different manufacturers."[56] In addition, to demonstrate that this latter requirement has been met, an ANDA must contain, at the time it is submitted, a "side-by-side comparison of the applicant's proposed labeling including, if applicable, any Medication Guide . . . with the approved labeling for the [RLD] with all differences annotated and explained."[57]

Under the FDCA, the term "labeling" refers to "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article."[58] This definition is very broad and has been interpreted by the FDA to encompass a wide array of materials created by a drug manufacturer for use by medical practitioners, pharmacists, and/or patients.[59] Specifically, where (as here) a drug product is subject to a risk management program that includes prescriber and patient education materials, the FDA has determined that all such materials are part of the product's labeling and subject to the statutory "same labeling" requirement.[60]

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[54] *See* 21 C.F.R. 314(d)(3) (stating that the FDA may not consider an ANDA to be received if the ANDA "is incomplete because it does not on its face contain information required under . . . section 505(j)).

[55] 21 U.S.C. 355(j)(2)(A)(vi) (referencing 355(b)(1)(F)); *see also* 21 C.F.R. 314.94(a)(8)(ii) (requiring an ANDA to contain, at the time it is submitted, "[c]opies of the label and all labeling for the drug product, including, if applicable, any Medication Guide.").

[56] 21 U.S.C. 355(j)(2)(A)(v). The changes allowed due to a difference in manufacturers are limited to "differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(5(F) of the act." 21 C.F.R. 314.94(a)(8)(iv).

[57] 21 C.F.R. 314.94(a)(8)(iv).

[58] 21 U.S.C. 321(m).

[59] *See* 21 C.F.R. 202.1(l)(2) (defining "labeling," as used in 21 U.S.C. 321(m), to include: "Brochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, sound recordings, exhibits, literature, and reprints and similar pieces of printed, audio, or visual matter descriptive of a drug and references published (for example, the 'Physicians Desk Reference') for use by medical practitioners, pharmacists, or nurses, containing drug information supplied by the manufacturer, packer, or distributor of the drug and which are disseminated by or on behalf of its manufacturer, packer, or distributor"). In addition, FDA regulations expressly define "labeling" to include Medication Guides and package inserts. *See* 21 C.F.R. 314.94(a)(8)(iv) ("Labeling (including . . . package insert, and, if applicable, Medication Guide) proposed for the [generic] drug product must be the same as the labeling approved for the [RLD].").

[60] *See* Letter from Janet Woodcock, Dir. CDER to Covington & Burling, LLP, *re: Docket No. 02P-0059/CP1*, Docket No. 02P-0059, p. 4 (Nov. 8, 2002) (stating that, with respect to Accutane, "the documents in the [risk management] program are part of product labeling" and "all generic [Accutane] manufacturers, as part of their labeling for ANDA approval, will have the same educational materials."). *Exhibit 27.*

The Xyrem Success Program is comprised of extensive written materials and visual aids that are shared with practitioners and patients to ensure that Xyrem is prescribed and used in a safe and effective manner. These materials, which were approved by the FDA as part of its approval of Xyrem, include the Xyrem Medication Guide, as well as (1) the Xyrem Success Program for Physicians informational booklet; (2) the "Dear Prescriber" Letter; (3) the Physician Enrollment Form; (4) the Xyrem Titration Schedule; (5) the Xyrem Success Program for Patients informational booklet; (6) the "Dear Patient" letter; (7) the Patient Enrollment and Prescription Form; and (8) the Xyrem Success Program for Patients Video.[61]

Under the relevant law and precedent, all of these materials constitute "labeling." And the FDA has previously recognized as much. For example, the FDA has expressly described the following aspects of the Xyrem Success Program as "labeling text": "the Product Package Insert, Medication Guide, Xyrem® Success Program For Physicians (Book, Letter and Registration Form), and Xyrem® Success Program for Physicians [sic][62] (Book, Letter, and Patient Prescription & Enrollment Form)."[63] The Agency has also affirmed that the program's "Patient Enrollment Form, Prescription Form, and Physician Registration form" are "labeling."[64] And it has referred to the script for the Xyrem Success Program for Patients Video as "labeling script."[65] Moreover, the Agency, on its website, describes changes to these materials—which Jazz has, on several occasions, submitted for Agency approval—as "Labeling Revision[s]."[66]

Because all of these Xyrem Success Program materials constitute "labeling," any ANDA referencing Xyrem must contain *all of them*, in order to be accepted for review by the FDA. As explained above, it is not sufficient for an ANDA applicant to promise that it will develop appropriate labeling in the future; it must provide actual samples of the labeling along with its application.[67] Moreover, each piece must be identical to the corresponding piece of Xyrem labeling, except for the limited allowable differences discussed *supra*.[68] And, to the extent that any of these materials do differ, in any way, from the Xyrem labeling, the ANDA must annotate and explain such differences.[69]

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[61] *See* Xyrem FDA Approved Labeling Text, Xyrem Risk Management Program, pp. 1-4 (Nov. 18, 2005), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2005/021196s005lbl.pdf; *see also* XYREM Success Program® for Physicians, *available at* http://www.xyrem.com/healthcare-professionals/success-program.

[62] The word "Physicians," here, should have read "Patients."

[63] Letter from Russell Katz, Dir. Division of Neurology Product, CDER to Orphan Medical, Inc., NDA 21-196/S-005, p. 1 (Nov. 18, 2005). *Exhibit 28.*

[64] Letter from Russell Katz, Dir. Division of Neurology Products, CDER to Jazz Pharmaceuticals, Inc., NDA 21-196/S-012, p. 1 (Nov. 13, 2006). *Exhibit 29.*

[65] Letter from Russell Katz, Dir. Division of Neurology Products, CDER to Jazz Pharmaceuticals, Inc., NDA 21-196/S-009, p. 1 (Jun. 30, 2006). *Exhibit 30.*

[66] *See* FDA, Approval History, NDA 021196, *available at* http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist. It should be noted that changes approved on November 18, 2005 were made in conjunction with the approval of a new indication and, therefore, are not separately listed as a "labeling revision."

[67] 21 U.S.C. 355(j)(2)(A)(vi) (referencing 21 U.S.C. 355(b)(1)(F)); 21 C.F.R. 314.101(d)(3); 21 C.F.R. 94(a)(8)(ii).

[68] 21 U.S.C. 355(j)(2)(A)(v); 21 C.F.R. 314.101(d)(3); 21 C.F.R. 94(a)(8)(ii).

[69] *See* 21 C.F.R. 314.94(a)(8)(iv).

If Roxane's ANDA did not contain, at the time of submission, all of the aforementioned pieces of labeling—appropriately devoid of any patent (or otherwise) protected information and accompanied by an annotated explanation of any differences—then it was improperly accepted for review. In fact, as explained above, it appears that Roxane's ANDA did not contain *any*, let alone all, of this material and information. For example, Roxane appears to concede that it did not provide the FDA with "sample patient and doctor forms that will be used to effectuate" its risk management system until October 19, 2011, despite the fact that such documents clearly constitute labeling.[70] Given this admission, and the many other aspects of the Xyrem Success Program that constitute labeling, it is clear that Roxane's ANDA did not contain the required labeling at the time it was filed. (In fact, it is possible that Roxane *still has not* provided all of the required labeling information to the FDA—though Jazz cannot know for sure, as it has not seen Roxane's submissions.) Consequently, Roxane's sodium oxybate ANDA should not have been accepted for review.

ii. An ANDA referencing Xyrem that does not contain a substantially complete proposed risk management system fails to meet the requirement for showing that its "conditions of use" have been previously approved.

In addition to the "same labeling" requirement, the FDA may not consider an ANDA to be received if the application does not, on its face, contain "information to show that the conditions of use . . . proposed for the new drug have been previously approved for" the RLD—in this case, Xyrem.[71] "In other words, a generic drug must have the same conditions of use as the innovator."[72] The phrase "'conditions of use' refer[s] to how, to whom, and for which purposes a drug product is used by physicians and patients."[73]

The elements of the Xyrem Success Program—which include, for example, (i) a restricted distribution program; (ii) a program to educate physicians and patients about the risks and benefits of Xyrem, including critical information necessary for the safe use and handling of the drug; and (iii) filling of the initial prescription only after the prescriber and patient have received and read the educational materials[74]—expressly restrict and control "how, to whom, and for which purposes [Xyrem] is used by physicians and patients." In fact, by definition, they are "needed to assure safe ***use*** of the drug."[75] Accordingly, and unquestionably, the elements of the Xyrem Success Program are "conditions of use" of Xyrem.

Because the elements of the Xyrem Success Program are "conditions of use" of Xyrem, any ANDA referencing Xyrem must contain, when filed, sufficient information to demonstrate that

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[70] *Roxane's Jan. 6, 2012 Letter* at 2.
[71] 21 U.S.C. 355(j)(2)(A)(i); *see also* 21 C.F.R. 314.101(b)(2); (d)(3) (listing, as one of the grounds for the FDA to refuse to file an ANDA, that the ANDA "does not on its face contain information required under . . . 505(j).").
[72] Federal Defendant's Memorandum in Opposition to Plaintiff's Motion for Temporary Restraining Order and/or Preliminary Injunction at 20, *ViroPharma Inc. v. Hamburg*, No. 12-00584 (D.D.C. filed on Apr. 17, 2012) (restating the meaning of 21 U.S.C. 355(j)(2)(A)(i) [hereinafter *FDA's ViroPharma Opposition Brief*]. *Exhibit 31.*
[73] *Id.*
[74] *Xyrem Approval Letter #1* at 2.
[75] 21 C.F.R. 314.520(a) (emphasis added).

the elements of its risk management system "have been previously approved for" Xyrem—i.e., are "the same as" Xyrem's.[76] An ANDA that does not contain a substantially complete risk management system would not be able to make this necessary showing and, thus, would not be acceptable for review by the FDA. Thus, given that Roxane's ANDA did not contain *any* risk management system at the time it was initially submitted (as Roxane appears to have conceded), it should not have been accepted for review.

b. It is inconsistent with the Hatch-Waxman Act for the FDA to accept for review an ANDA referencing Xyrem that does not contain a substantially complete, proposed risk management system.

Where an RLD is subject to a patent-protected risk management system—as is the case here—the acceptance for review of an ANDA that does not contain a substantially complete proposed risk management system not only violates the aforementioned regulatory provisions; it also is fundamentally inconsistent with the protections that the Hatch-Waxman Act was intended to provide to both patent holders and generic applicants.

In the Hatch-Waxman Act, Congress created a comprehensive framework for resolving patent disputes relating to ANDAs. An ANDA that references a listed drug must include a certification regarding each patent applicable to the listed drug.[77] When the ANDA includes a certification that a given patent is invalid or will not be infringed (a "paragraph IV certification"), the applicant must give notice of such certification to the patent owner and NDA holder for the listed drug. This notice must be provided within twenty days from when the FDA informs the applicant that its ANDA has been accepted for review, and it must contain a detailed statement of the factual and legal basis for the patent challenge.[78]

The Hatch-Waxman Act makes the filing of an ANDA with a paragraph IV certification an act of infringement[79] and, upon receipt of the paragraph IV notice, the patentee has forty-five days

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[76] In approving Xyrem with "restrictions to assure safe use" under Subpart H, the FDA necessarily concluded that Xyrem "can be safely used ***only*** if distribution or use is restricted." 21 C.F.R. 314.520(a) (emphasis added). Accordingly, the specific restrictions the FDA required were, by definition, "needed to assure safe use" of Xyrem. *Id.* It necessarily follows that a generic copy of Xyrem would likewise need the same restrictions in order to be approved, as it would otherwise be unsafe. Moreover, where an innovator drug has a REMS, any ANDA product referencing the innovator product is subject to the following aspects of its REMS, to the extent they exist: 1) the Medication Guide and patient package insert; and (2) any ETASU. *See* 21 U.S.C. 355-1(i)(1); *see also, e.g.,* Letter from Keith Webber, Deputy Dir. Office of Pharmaceutical Science, CDER to Mylan Pharmaceuticals, p. 2 (Mar. 27, 2012) ("Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS.") (citing section 505-1(i) of the FDCA), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/090323s000ltr.pdf. And, where a generic drug is subject to a REMS, the ANDA for that drug will not be approved until all required aspects of the REMS are in place. *See* FDA, Questions and Answers on the Federal Register Notice on Drugs and Biological Products Deemed to Have Risk Evaluation and Mitigation Strategies (noting that, where a REMS is required, FDA "will not approve/license the product without a REMS"), *available at* http://www.fda.gov/RegulatoryInformation/Legislation /FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095439.htm.

[77] *See* 21 U.S.C. 355(j)(2)(A)(vii).

[78] *See* 21 U.S.C. 355(j)(2)(B).

[79] *See* 35 U.S.C. 271(e)(2)(A).

to bring suit against the ANDA applicant for patent infringement.[80] If the patentee does not sue, the FDA may proceed to review and make an approval decision on the ANDA. If the patentee does file suit, the FDA may not approve the ANDA until expiration of the patent, resolution of the suit, or the elapsing of thirty months after receipt of the notice (the "Hatch-Waxman 30-month stay"), whichever comes first.[81]

This framework is predicated on an important and fundamental presumption: that ANDA-related patent disputes will be ripe for adjudication at the time the ANDA is filed—i.e., when the FDA accepts it for review. As the FDA has noted, Congress, in creating the Hatch-Waxman framework, did "not intend that applicants be permitted to circumvent [the framework] by filing sham ANDA's or ANDA's which are substantially incomplete."[82] In other words, Hatch-Waxman only works if all elements of an ANDA that implicate patents listed with the RLD are sufficiently developed, at the time of filing, to enable judicial review. Thus, while the FDA is not itself responsible for adjudicating patent disputes, the Agency does play a critical gatekeeping function to "ensure[] that the statutory litigation triggers do not result in unnecessary patent infringement litigation initiated by incomplete ANDAs."[83]

Here, Roxane engaged in exactly the type of "submit-first, fix-later" strategy about which Congress was concerned, with predictably troubling results. As discussed above, Roxane's initial ANDA submission apparently did not include *any* proposed risk management system. But it did contain a paragraph IV certification, in which Roxane asserted, *inter alia*, that its ANDA would not infringe Jazz's Xyrem Success Program-related patents. Thus, acceptance of Roxane's ANDA for review triggered the process for litigating those patents (along with the other patents listed for Xyrem in the Orange Book). Roxane subsequently provided the requisite paragraph IV notice to Jazz, and Jazz then filed a patent infringement suit within the 45-day period provide by statute.

Jazz was compelled to file suit at this time because, under the Hatch-Waxman framework, this was the only way for Jazz to ensure that it would have the opportunity to litigate its claims before Roxane's potentially infringing generic product entered the market. But the very thing that potentially infringed on Jazz's Xyrem Success Program-related patents—Roxane's risk management system—did not yet exist, even, apparently, on paper. In fact, it was not until approximately ten months after Roxane had initially submitted its ANDA, and well after litigation had commenced, that Roxane reportedly submitted to FDA its bare-bones, six-page outline of a potential risk management system.[84] And, according to Roxane itself, another six months elapsed before Roxane supplemented its ANDA to include anything arguably resembling a substantially complete risk management system proposal.[85] In sum, the parties

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[80] 21 U.S.C. 355(j)(5)(B)(iii).
[81] *Id.*
[82] Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions; Final Rule, 59 Fed. Reg. 50,338, 50,349 (Oct. 3, 1994) (quoting H.R. REP. NO. 98-857, pt. 1, 24 (1984)).
[83] *SB Pharmco Puerto Rico, Inc. v. Mut. Pharm. Co., Inc.*, 552 F. Supp. 2d 500, 508 (E.D. Pa. 2008).
[84] *See Jazz's Jan 19, 2012 Letter* at 2.
[85] Moreover, Roxane did not disclose its supplement to Jazz, or produce the relevant documents in the litigation, until 6 weeks after it had been submitted to the FDA. *See Jazz's Dec. 20, 2011 Letter* at 2. These documents have been submitted confidentially to the FDA and are not publicly available.

were almost a year into Hatch-Waxman litigation before one of the very things key to resolution of the litigation—Roxane's risk management system—had become part of Roxane's ANDA.

As a result of the improper acceptance of Roxane's ANDA, Jazz has been compelled to put its patent portfolio at risk—and expend significant financial and other resources—prematurely and, perhaps, unnecessarily (depending on the risk management system to which Roxane's drug product may ultimately be subject). Moreover, the premature acceptance of Roxane's ANDA caused the Hatch-Waxman thirty-month stay to begin too soon. The thirty-month stay is designed to provide adequate time for the patent infringement action to be litigated in court, and to give assurances to innovator companies that generic manufacturers will not immediately proceed to market after receiving approval of their ANDAs.[86] Roxane, however—contrary to Congress's express prohibition—was "permitted to circumvent [the Hatch-Waxman framework] by filing [an ANDA which is] substantially incomplete."[87] And this "bait-and-switch" maneuver has complicated, and will likely delay, resolution of the patent litigation, as it effectively frustrated the ripening of the dispute for at least a year. This, in turn, increases the probability that the litigation will not be resolved prior to the expiration of the 30-month stay, and thus increases the likelihood that Jazz will face a competing, and potentially infringing, product in the market before it has had the chance to fully litigate its claims—a result that would be highly prejudicial to Jazz, and wholly inconsistent with the policies underlying the Hatch-Waxman Act.

Similarly, Jazz would be significantly prejudiced if, after litigating whether the current incarnation of Roxane's proposed system infringes Jazz's patents, Roxane's generic product is later approved with a risk management system materially different from that currently proposed, but which nonetheless infringes on Jazz's patents. Jazz would have to file another lawsuit, but this time without the benefit of the Hatch-Waxman 30-month stay, and, potentially, *after* the offending product is already on the market.

Finally, Jazz is not the only party that has been prejudiced by the FDA's premature acceptance of Roxane's ANDA. Any other ANDA applicants seeking to market their own generic versions of Xyrem have been prejudiced, as well. A generic sodium oxybate product's risk management system is essential to ensuring patient safety. And developing an effective system requires significant time and resources. In accepting Roxane's ANDA before Roxane had developed such a critical product aspect, the FDA effectively rewarded Roxane's bait-and-switch gambit at the expense of all other generic manufacturers that may, instead—and appropriately—have been expending the resources to develop a risk management system consistent with the Xyrem Success Program prior to submitting their ANDAs (as required by the plain text of the regulations and prior FDA practice, as discussed *supra*). Roxane's maneuver is entirely

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[86] *See* 180-Day Generic Drug Exclusivity for Abbreviated New Drug Applications; Proposed Rule, 64 Fed. Reg. 42,873, 42,881 (Aug. 6, 1999) ("The 30-month period . . . is intended to give innovator companies assurance that generic manufacturers would not file ANDA's with paragraph IV certifications and then immediately market the generic drug product. . . . The legislative history of the amendments makes clear that the 30-month stay of approval was intended to correspond as closely as possible with the expected duration of a patent infringement suit, and to provide protection to innovator companies during that time.").

[87] Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions; Final Rule, 59 Fed. Reg. 50,338, 50,349 (Oct. 3, 1994) (quoting H.R. REP. NO. 98-857, pt. 1, 24 (1984)).

inconsistent with congressional intent and FDA's public policy goals. If Roxane's incomplete ANDA is allowed to stand, it will serve to encourage other applicants to attempt to similarly circumvent the regulatory requirements in the future.

2. **The FDA should rescind its acceptance of Roxane's ANDA, and decline to accept for review any ANDA referencing Xyrem—from Roxane or any other applicant—unless and until such ANDA contains a substantially complete risk management system proposal demonstrating that the proposed ANDA drug product would have the same labeling and conditions of use as Xyrem.**

Though Jazz does not have access to Roxane's ANDA, one thing is clear from Roxane's public statements: Roxane's sodium oxybate ANDA did not contain, at the time it was submitted, a proposed risk management system—despite the fact that Xyrem is subject to such a system, and that aspects of Xyrem's system constitute labeling and conditions of use. As a result, Roxane's ANDA could not, and did not, comply with certain generally-applicable requirements for filing an ANDA—namely, that the ANDA must demonstrate that it would have the same labeling and conditions of use as the RLD (here, Xyrem).[88] The FDA's acceptance of such a facially deficient ANDA was thus contrary to the governing law. Moreover, as discussed above, it was inconsistent with the prior FDA practice, at odds with the policy goals underlying the Hatch-Waxman framework, and prejudicial to Jazz and other potential ANDA applicants. The FDA should rescind the acceptance of Roxane's ANDA (and any other similarly situated ANDA referencing Xyrem). And the FDA should not again accept any ANDA referencing Xyrem (including Roxane's) for review unless and until it complies with *all* of the requirements for a reviewable ANDA.

3. **The FDA should rescind its acceptance of Roxane's ANDA, even if Roxane has since provided the FDA with information sufficient to demonstrate that Roxane's generic Xyrem product would have the same labeling and conditions of use as Xyrem.**

It is conceivable, but unlikely (based on Roxane's public statements), that—although Roxane's initial ANDA submission did not demonstrate that Roxane's generic drug product had the same labeling and conditions of use as Xyrem—Roxane subsequently provided to the FDA information sufficient to make this showing.[89] But, even if this is the case, the FDA should

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[88] For example, as discussed *supra*, Roxane has apparently conceded that it did not provide FDA with "sample patient and doctor forms that will be used to effectuate" its risk management system until October 19, 2011, despite the fact that the Xyrem Success Program contains such pieces of labeling, which Roxane's ANDA must copy because it references Xyrem. *Roxane's Jan. 6, 2012 Letter* at 2.

[89] The only submission of which Jazz is aware that could even conceivably have reached this threshold is Roxane's October 19, 2011 submission, which provided, for the first time, a detailed description of Roxane's proposed risk management system. *Roxane's Jan. 6, 2012 Letter* at 2. For, as Roxane has conceded, until this document was submitted, at least the following central features of its proposed risk management system had not been revealed to the FDA: (1) identification of the "specific pharmaceutical distributor that will be responsible for carrying out the tasks," (2) "sample patient and doctor forms that will be used to effectuate the elements" of the risk management system; and (3) "a mock-up of the website that Roxane will use to communicate with physicians, pharmacists, and patients." *Id.* However, it is also quite plausible that even this submission did not comply with the detailed statutory and regulatory requirements for demonstrating that an ANDA would have *the same* labeling and

nonetheless rescind Roxane's ANDA, for subsequent submissions cannot "cure" an ANDA that was deficient, on its face, when initially filed. For the FDA to allow otherwise (and permit Roxane to maintain the benefit of its original filing date) would be to enable Roxane, contrary to Congress's express wishes and the FDA's prior practice, to "circumvent" the Hatch-Waxman framework in a manner that is prejudicial to Jazz and other potential ANDA sponsors.[90]

Again, Jazz has been prejudiced by the improper acceptance of Roxane's ANDA, because it has caused the related patent infringement litigation to begin prematurely. Rescinding the acceptance of Roxane's ANDA, and requiring Roxane to re-file its ANDA once it contains, for the first time, a risk management system would be an equitable result that might mitigate the harm Jazz has suffered. The new filing would, of course, trigger all of the requirements associated with an ANDA filing, including the requirements that Roxane provide new certifications to all patents listed for Xyrem in the Orange Book,[91] and provide notice to Jazz of any such new certifications that are paragraph IV certifications.[92] Upon receipt of such notice, Jazz would then be able to consider the potentially infringing nature of Roxane's risk management system before filing suit (and thereby starting a new 30-month Hatch-Waxman stay period[93])—an opportunity Jazz was unfairly and unreasonably denied in the first instance. Moreover, to the extent that Jazz decided to file suit, there would actually exist a potentially infringing system to address in the litigation, and Jazz would be more likely to have the opportunity to fully litigate its claims before facing a potentially infringing product in the market—as Congress intended.

III. CONCLUSION

For all 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 the petition will be provided upon request.

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previously-approved conditions of use, which are discussed *supra* (again, because it does not have access to this submission, Jazz cannot know for sure).

[90] *See* Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions; Final Rule, 59 Fed. Reg. 50,338, 50,349 (Oct. 3, 1994) (quoting H.R. REP. NO. 98-857, pt. 1, 24 (1984)).

[91] *See* 21 U.S.C. 355(j)(2)(A)(vii).

[92] *See* 21 U.S.C. 355(j)(2)(B).

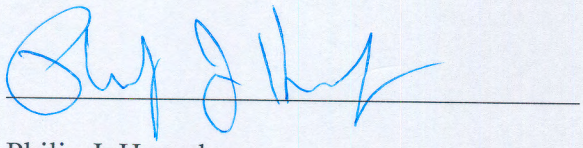
[93] *See* 21 U.S.C. 355(j)(5)(B)(iii).

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: December 20, 2011 (correspondence with the Court regarding Roxane's delay in submitting a proposed restricted distribution system to its ANDA and to Jazz); January 6, 2012 (correspondence with the Court, in which Roxane appears to have conceded that its ANDA referencing Xyrem did not contain, when filed, a proposed restricted distribution system); January 19, 2012 (correspondence with the Court regarding Roxane's delay in submitting a proposed restricted distribution system to its ANDA and to Jazz). 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,



Philip J. Honerkamp
Vice President, Strategic Operations
Jazz Pharmaceuticals, Inc.
3180 Porter Drive
Palo Alto, CA 94304
(650) 496-2611

on behalf of Jazz Pharmaceuticals, Inc.

Citizen Petition – Index of Exhibits

Exhibit:

1) **Footnote 2:** Beusterien KM, Rogers AE, Walsleben JA, Emsellem HA, Reblando JA, Wang L, Goswami M, Steinwald B. Health-related quality of life effects of modafinil for treatment of narcolepsy. *Sleep*. 1999 Sep 15;22(6):757-65.

2) **Footnote 3:** Letter from Robert Temple, Dir. Office of Drug Evaluation, CDER to Orphan Medical, Approval Letter for Xyrem, NDA 21-196 (Jul. 17, 2002).

3) **Footnote 4:** 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.

4) **Footnote 5:** 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. Review.

5) **Footnote 6:** Nordenberg T. The death of the party: All the rave, GHB's hazards go unheeded. *FDA Consum*. 2000 Mar-Apr;34(2):14-16, 18-19.

6) **Footnote 7:** 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), *available at* http://www.fda.gov/ohrms/dockets/ac/01/slides/3754s1.htm. **Pages 2-4 and 6-167 of Exhibit 6 have been removed as irrelevant, per the requirement codified at 21 C.F.R. § 10.20(c)(3).**

7) **Footnote 9:** Nicholson KL, Balster RL. GHB: a new and novel drug of abuse. *Drug Alcohol Depend*. 2001 Jun 1;63(1):1-22. Review.

8) **Footnote 9:** Schwartz RH, Milteer R, LeBeau MA. Drug-facilitated sexual assault ('date rape'). *South Med J*. 2000 Jun;93(6):558-61. Review.

Exhibit:

9) **Footnote 12:** Letter from David Satcher, Asst. Secretary for Health and Surgeon General, HHS to Donnie R. Marshall, Deputy Administrator, DEA (May 19, 1999), *available at* http://www.deadiversion.usdoj.gov/fed_regs/rules/2000/fr0313.htm.

10) **Footnote 14:** 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).

11) **Footnote 15:** JODY COREY-BLOOM & RONALD DAVID, CLINICAL ADULT NEUROLOGY 180 (2008). **Pages 1-179 and 181-484 of Exhibit 11 have been removed as irrelevant, per the requirement codified at 21 C.F.R. § 10.20(c)(3).**

12) **Footnote 16:** 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.

13) **Footnote 17:** Broughton WA, Broughton RJ. Psychosocial Impact of Narcolepsy, *Sleep.* 1994 Dec;17(8Suppl):S45-9. Review.

14) **Footnote 17:** Roger Broughton & Quais Ghana, *The Impact of Compound Narcolepsy on the Life of the Patient, in* NARCOLEPSY 201, 201-20 (Christian Guilleminault et al. eds., 1976).

15) **Footnote 31:** XYREM Success Program® for Physicians, *available at* http://www.xyrem.com/healthcare-professionals/success-program.

16) **Footnote 34:** U.S. Patent No. 7,668,730 (filed Feb. 23, 2010).

17) **Footnote 34:** U.S. Patent No. 7,765,106 (filed Jul. 27, 2010).

18) **Footnote 34:** U.S. Patent No. 7,765,107 (filed Jul. 27, 2010).

19) **Footnote 34:** U.S. Patent No. 7,895,059 (filed Feb. 22, 2011).

Exhibit:

20) **Footnote 38:** Letter from Randall S. Wilson, Vice President, Scientific, Medical and Regulatory Affairs, Roxane Laboratories, Inc. to Jazz Pharmaceuticals, *re: Patent Notice Pursuant to 505(b)(3)(B) [21 U.S.C. § 355(b)(3)(B)]*, pp. 1-11 (Oct. 14, 2010).

21) **Footnote 40:** U.S. Patent Nos. 7,851,506 (filed Dec. 14, 2010).

22) **Footnote 40:** Letter from Randall S. Wilson, Vice President, Scientific, Medical and Regulatory Affairs, Roxane Laboratories, Inc. to Jazz Pharmaceuticals, *re: Patent Notice Pursuant to § 505(j)(2)(B)(ii) [21 USC § 355(j)(2)(B)(ii)]*, pp. 1-7 (Mar. 22, 2011).

23) **Footnote 40:** Letter from Randall S. Wilson, Vice President, Scientific, Medical and Regulatory Affairs, Roxane Laboratories, Inc. to Jazz Pharmaceuticals, *re: Patent Notice Pursuant to § 505(j)(2)(B)(ii) [21 USC § 355(j)(2)(B)(ii)]*, pp. 1-3 (Jan. 10, 2011).

24) **Footnote 41:** Letter from Theodora McCormick, Sills Cummis & Gross, PC to the Honorable Cathy L. Waldor, U.S.M.J., *re: Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*, No. 10-6108, p. 3, n.1 (Jan. 6, 2012).

25) **Footnote 42:** Letter from Charles M. Lizza, Saul Ewing, LLP to the Honorable Cathy L. Waldor, U.S.M.J., *re: Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*, No. 10-6108, p. 2 (Jan. 19, 2012).

26) **Footnote 46:** Letter from Charles M. Lizza, Saul Ewing, LLP to the Honorable Cathy L. Waldor, U.S.M.J., *re: Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*, No. 10-6108, p. 2 (Dec. 20, 2011).

27) **Footnote 60:** Letter from Janet Woodcock, Dir. CDER to Covington & Burling, LLP, *re: Docket No. 02P-0059/CP1*, Docket No. 02P-0059, p. 4 (Nov. 8, 2002).

28) **Footnote 63:** Letter from Russell Katz, Dir. Division of Neurology Product, CDER to Orphan Medical, Inc., NDA 21-196/S-005, p. 1 (Nov. 18, 2005).

Exhibit:

29) **Footnote 64:** Letter from Russell Katz, Dir. Division of Neurology Products, CDER to Jazz Pharmaceuticals, Inc., NDA 21-196/S-012, p. 1 (Nov. 13, 2006).

30) **Footnote 65:** Letter from Russell Katz, Dir. Division of Neurology Products, CDER to Jazz Pharmaceuticals, Inc., NDA 21-196/S-009, p. 1 (Jun. 30, 2006).

31) **Footnote 72:** Federal Defendant's Memorandum in Opposition to Plaintiff's Motion for Temporary Restraining Order and/or Preliminary Injunction at 20, *ViroPharma Inc. v. Hamburg*, No. 12-00584 (D.D.C. filed on Apr. 17, 2012).