



DEC 13 2012

• Philip J. Honerkamp
Vice President, Strategic Operations
Jazz Pharmaceuticals, Inc.
3180 Porter Drive
Palo Alto, CA 94304

Re: Docket No. FDA-2012-P-0733

Dear Mr. Honerkamp:

This letter responds to your citizen petition (petition) received July 10, 2012,¹ in which you request the U.S. Food and Drug Administration (FDA, or agency) to: (1) rescind the acceptance of any previously accepted abbreviated new drug application (ANDA) referencing XYREM, including an ANDA filed by Roxane Laboratories, Inc. (Roxane), that did not contain, at the time it was accepted for review, a proposed risk management system that provides information sufficient to demonstrate the same labeling and 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 that provides information sufficient to demonstrate the same labeling and conditions of use as XYREM; and (3) if the sponsor 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 does contain a proposed risk management system sufficient to demonstrate the same labeling and conditions of use as XYREM, not approve the ANDA for a period of up to thirty months beginning on the date that Jazz Pharmaceuticals, Inc. (Jazz) receives notice of any Paragraph IV certifications contained in the new ANDA, if Jazz avails itself of its right to initiate a patent infringement action based on the notice.²

FDA has considered the information provided in your petition, as well as other information available to the Agency and the relevant statute and regulations, and for the reasons set forth below, the petition is denied.

I. BACKGROUND

A. XYREM

¹ Citizen Petition submitted by P. J. Honerkamp on behalf of Jazz Pharmaceuticals, Docket No. 2012-P-0733 (July 10, 2012).

² Id., at 1-2.

On July 17, 2002, FDA approved new drug application (NDA) 21-196 for XYREM oral solution for the treatment of cataplexy in patients with narcolepsy, and on November 18, 2005, FDA approved a supplemental new drug application (sNDA) for XYREM oral solution for the treatment of excessive daytime sleepiness in patients with narcolepsy.

The active ingredient in XYREM is sodium oxybate, which is a central nervous system depressant. Sodium oxybate is the sodium salt of gamma-hydroxybutyrate (GHB). GHB is a schedule I controlled substance due to its abuse as a recreational drug, lack of currently accepted medical use in treatment, and lack of an accepted safe use under medical supervision.³ Recreational abuse of GHB has been associated with adverse CNS events, including life-threatening respiratory depression, coma, and death.⁴ GHB is the pharmacologically active metabolite of gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD), both of which have also been abused recreationally.⁵

XYREM is a schedule III controlled substance that has been associated with confusion, depression, and other neuropsychiatric events.⁶ XYREM's approval was therefore subject to the following post-marketing restrictions necessary to assure its safe use:

1. restricted distribution;
2. a program to educate physicians and patients about the risks and benefits of XYREM, including a requirement to provide critical information necessary for the safe use and handling of the drug;
3. a requirement that initial prescriptions for XYREM can be filled only if the prescriber and patient have both received and read the educational materials; and
4. maintenance of a registry of all patients prescribed XYREM, and a record of all prescribers.⁷

FDA also required XYREM's sponsor to make a Medication Guide for this drug product available for every patient to whom it was prescribed, and to include on the label of each

³ 21 U.S.C. 812(b)(1).

⁴ Okun, MS; Boothby, LA; Bartfield, RB; and Doering PL. GHB: an important pharmacologic and clinical update. *J Pharm Pharm Sci.* 2001 May-Aug; 4(2):167-7; Lenz, D; Rothschild, MA; Kroner, L. Intoxications due to ingestion of gamma-butyrolactone: organ distribution of gamma-hydroxybutyric acid and gamma-butyrolactone. *Ther Drug Mani.* 2008 Dec; 30(6):755-61; Nicholson, KL; Balster, RL. GHB: a new and novel drug of abuse. *Drug Alcohol Depend.* 2001 Jun 1; 63(1):1-22; Schwartz, RH; Milteer, R; LeBeau, MA. Drug-facilitated sexual assault. *South Med J.* 2000 Jun; 93(6):558-61.

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

⁶ 21 U.S.C. 812(b)(3); XYREM Package Insert, at 1, 10, available at

<http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=926eb076-a4a8-45e4-91ef-411f0aa4f3ca>

⁷ 21 CFR 314.520; Letter to D. Reardon, VP Reg. Affairs, Orphan Medical fr. R. Temple, CDER re NDA 21-196, at 2 (July 17, 2002) (Approval Letter for XYREM).

carton container of the product a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient dispensed XYREM, and a statement about how the Medication Guide is to be provided.⁸ XYREM's labeling also includes a boxed warning stating that sodium oxybate is GHB, which is a known drug of abuse that has been associated with CNS adverse events, including death.⁹

XYREM's sponsor, Jazz Pharmaceuticals, Inc. (Jazz), implemented these FDA-mandated restrictions on XYREM's distribution and use through the XYREM Success Program, which was known initially as a "Risk Management Program."¹⁰ XYREM was approved before the enactment of the Food and Drug Administration Amendments Act of 2007 (FDAAA),¹¹ but was deemed to have in effect a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU).¹² The XYREM Success Program is therefore a deemed REMS with ETASU.¹³

The XYREM Success Program includes: (1) a Medication Guide, (2) a XYREM Success Program for Physicians informational booklet, (3) a "Dear Prescriber" Letter, (4) a Physician Enrollment Form, (5) a XYREM Titration Schedule, (6) a XYREM Success Program for Patients informational booklet, (7) a "Dear Patient" letter, (8) a Patient Enrollment and Prescription Form, and (9) a XYREM Success Program for Patients Video.¹⁴

The XYREM Success Program also includes several mechanisms for tightly controlling, tracking, and monitoring access to the product. Prescribers and patients must enroll in the XYREM Success Program before they can prescribe or use the drug.¹⁵ XYREM is then dispensed only through a central pharmacy, using a central database. This ensures that only registered prescribers and patients have access to the product, and allows the pharmacy to track product shipment and delivery and monitor usage and refill patterns to identify potential misuse, abuse, or diversion.¹⁶

⁸ Approval Letter for XYREM, page 2.

⁹ XYREM labeling approved November 18, 2005; 21 CFR 201.57(c)(1).

¹⁰ Approval Letter for XYREM, pages 1-2.

¹¹ Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act (FDAAA) of 2007, Public Law Number 110-85.

¹² Section 909(b)(2) of FDAAA; draft guidance for industry *Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications*, at 4-5 (Sept. 2009), available on the Internet at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> (REMS Guidance).

¹³ 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, 73 FR 16313-16314 (March 27, 2008).

¹⁴ XYREM materials approved November 18, 2005, which includes the XYREM Medication Guide; XYREM Success Program for Physicians, available on the Internet at <http://www.xyrem.com/healthcare-professionals/success-program>; and XYREM Success Program for Patients, available on the Internet at <http://www.xyrem.com/patient-success-program>.

¹⁵ Id.

¹⁶ XYREM Medication Guide, pages 1-4.

Several aspects of the XYREM Success Program are the subject of patents listed in the FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* publication (the "Orange Book").¹⁷

B. Applicable Statutory and Regulatory Framework

1. *Abbreviated New Drug Applications*

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) created section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), which established the current ANDA approval process.¹⁸ To obtain approval, an ANDA applicant is not required to submit evidence of the safety and effectiveness of the drug product, as is required for an NDA. Instead, the ANDA relies on FDA's previous finding that the reference listed drug (RLD) is safe and effective.¹⁹ Section 505(j)(2) sets out requirements for ANDA approval. In particular, the ANDA applicant must identify the listed drug on which it seeks to rely and, with limited exceptions, a drug product described in an ANDA must contain the same active ingredient, route of administration, dosage form, and strength as the listed drug it references.²⁰ An ANDA applicant also must demonstrate that its proposed drug product is bioequivalent to the RLD.²¹

An ANDA must include information to show that the conditions of use prescribed, recommended, or suggested in the labeling for the proposed generic drug product have been previously approved for the RLD.²²

In addition, ANDAs must contain information to show that the proposed labeling is the same as the labeling approved for the RLD, except for permitted differences that are required because of differences in the product approved under what is commonly referred to as a "suitability" petition, or because the proposed drug product and the RLD are produced by different manufacturers.²³ To fulfill this "same labeling" requirement, the ANDA applicant must submit a copy of the labeling for the RLD, copies of the proposed labeling, and a side-by-side comparison of the proposed labeling and the labeling for the

¹⁷ U.S. Patent Nos. 7,668,730; 7,765,106; 7,765,107; and 7,895,059.

¹⁸ Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585.

¹⁹ A reference listed drug (RLD) is "the listed [i.e., approved] drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application" (21 CFR 314.3). RLDs are identified in the Orange Book.

²⁰ Section 505(j)(2)(A) of the FD&C Act; 21 CFR 314.94(a). See also section 505(j)(4) of the FD&C Act (directing FDA to approve an ANDA unless agency determines information required in 505(j)(2) is insufficient).

²¹ See section 505(j)(8)(B)(i) of the FD&C Act. See also 21 CFR 320.1(e) and 320.23(b).

²² Section 505(j)(2)(A)(i) of the FD&C Act; 21 CFR 314.94(a)(4).

²³ Section 505(j)(2)(A)(v) and 505(j)(4)(G) of the FD&C Act; 21 CFR 314.94(a)(8).

RLD with all differences annotated and explained.²⁴ Required labeling includes the container label, package insert, and, if applicable, any Medication Guide for the RLD.²⁵

2. *Patent Certification and Notice Requirements*

Section 505(b)(1) of the FD&C Act requires NDA sponsors to submit with their application:

the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug.²⁶

Upon approval of the NDA, FDA publishes this patent information in the Orange Book. ANDA applicants must provide one of four certifications with respect to each of the patents listed in the Orange Book for the RLD.²⁷ In what is referred to as “a paragraph IV certification,” the ANDA applicant asserts that the listed patents are invalid or will not be infringed by its drug product.²⁸ The ANDA applicant is required to provide the NDA holder and patent owner with notice of a paragraph IV certification, and a detailed statement of the factual and legal basis of an opinion of the applicant that the patent is invalid or will not be infringed, no later than 20 days after the date of the postmark on the notice from FDA that the agency has received the application for review, as described in detail below.²⁹ The NDA holder or patent owner then has 45 days to file a patent infringement suit against the ANDA applicant, and if a suit is filed, FDA may not approve the ANDA for 30 months, unless a court orders otherwise (referred to as the “thirty-month stay”).³⁰ FDA regulations provide that if the notice is deemed inadequate by the patent owner and the ANDA applicant subsequently amends both the notice and the ANDA to indicate that the date of notice should be amended, FDA may adjust the 45-day clock to begin as of the date the patent holder receives the amended notice.³¹ If an ANDA applicant that has filed a paragraph IV certification and has provided notice to the RLD sponsor wishes to share sensitive information in its ANDA with the RLD sponsor, section 505(j)(5)(C)(i)(III) of the FD&C Act sets forth a procedure under which the applicant is to allow the NDA sponsor or patent owner to review its ANDA, while maintaining the confidentiality of the information contained in it.

²⁴ 21 CFR 314.94(a)(8)(i)-(iv).

²⁵ 21 CFR 314.94(a)(8)(iv).

²⁶ Section 505(b)(1) and (c)(2) of the FD&C Act.

²⁷ Section 505(j)(2)(A)(vii) of the FD&C Act.

²⁸ Id.

²⁹ Section 505(j)(2)(B) of the FD&C Act.

³⁰ Section 505(j)(5)(B)(iii) of the FD&C Act.

³¹ 21 CFR 314.95(c), (f); see also *Abbreviated New Drug Application Regulations, Patent and Exclusivity Provisions; Final Rule*, 59 FR 50338, 50349 (Oct. 3, 1994) (Patent and Exclusivity Final Rule) (discussing promulgation of the regulation).

FDA has long held the position that the agency plays only a ministerial role with respect to these patent listing, certification, and notice requirements,³² which position has been upheld by the courts.³³

3. *ANDA Receipt for Filing*

After an ANDA is submitted to FDA, the Agency reviews it to determine whether FDA will “receive” the ANDA for review.³⁴ FDA’s receipt of an ANDA “means that FDA has made a threshold determination that the abbreviated application is sufficiently complete to permit a substantive review.”³⁵ FDA’s regulations set forth several bases on which the Agency has discretion to refuse to receive an ANDA for review. For example, FDA “may” refuse to receive an ANDA if the application is not submitted in the form required under 21 CFR 314.94, it does not include a complete environmental assessment, or because it does not “on its face contain information required” under section 505(j) and 21 CFR 314.94.³⁶ The regulation also provides two express bases on which FDA “will” refuse to receive an ANDA: (1) if the proposed product is a biological product subject to licensing under the Public Health Service Act, or (2) the RLD is entitled to a 5-year period of exclusivity under section 505(j)(4)(D)(ii) of the FD&C Act, unless the 5-year exclusivity period has elapsed or unless four years of the 5-year period have elapsed and the ANDA contains a certification of patent invalidity or noninfringement described in 314.94(a)(12)(i)(A)(4).³⁷

4. *REMS*

The Food and Drug Administration Amendments Act (FDAAA) was enacted on September 27, 2007.³⁸ Title IX, Subtitle A, section 901 of FDAAA created section 505-1 of the FD&C Act, which applies to applications for the approval of prescription drugs submitted under subsections 505(b) or (j), and applications submitted under section 351 of the Public Health Service Act. Section 505-1 authorizes FDA to require applicants to submit a proposed REMS as part of their application if FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh its risks.³⁹

A REMS for an NDA or biologics license application (BLA) must have a timetable for submission of assessments of the REMS,⁴⁰ and may include additional elements, including a Medication Guide, a patient package insert, a communication plan to health care providers, or ETASU.⁴¹

³² See Patent and Exclusivity Final Rule, 59 FR at 50349.

³³ See, e.g., *aaiPharma v. Thompson*, 296 F.3d 227, 242-43 (4th Cir. 2002); *American Biosci., Inc. v. Thompson*, 269 F.3d 1077, 1084 (D.C. Cir. 2001).

³⁴ 21 CFR 314.101(b)(1).

³⁵ *Id.*

³⁶ 21 CFR 314.101(d)(1)-(9).

³⁷ 21 CFR 314.101(e).

³⁸ Public Law Number 110-85.

³⁹ Section 505-1(a)(1) of the FD&C Act.

⁴⁰ Section 505-1(d) of the FD&C Act.

⁴¹ Sections 505-1(e) and 505-1(f)(1) of the FD&C Act.

ETASU may be required as part of a REMS if a drug has been shown to be effective, but has been associated with one or more serious adverse events and can only be approved if, or would be withdrawn unless, the required ETASU are part of a strategy to mitigate the specific serious risks listed in the labeling of the product.⁴² Before ETASU may be required for products initially approved without ETASU, FDA must determine that a timetable for assessment, Medication Guide, patient package insert, or communication plan are not sufficient to mitigate these risks.⁴³ The holder of an approved application is prohibited from using any ETASU required by FDA to block or delay approval of an ANDA or an application under 505(b)(2).⁴⁴

Previously approved drug products that as of the effective date of FDAAA had in effect restrictions to assure safe use required under 21 CFR 314.520 or 601.42, or otherwise agreed to by the applicant and the Secretary, were “deemed to have in effect an approved risk evaluation and mitigation strategy under section 505-1 of the [FD&C Act].”⁴⁵ FDA published a list of drugs in the *Federal Register* that were deemed to have an approved REMS on March 27, 2008, and directed holders of approved applications for those products to submit a proposed REMS by September 21, 2008.⁴⁶ These proposed REMS are subject to section 505-1 of the FD&C Act as if included in an application at the time the application was submitted.⁴⁷

The statute provides that an ANDA referencing an RLD subject to a REMS may only be required to have a Medication Guide or patient package insert and ETASU, if the RLD has a REMS with these elements.⁴⁸ An ANDA applicant and the holder of the approved NDA for the referenced RLD are required to use a single, shared system for the ETASU, except that FDA may waive the requirement for a single, shared system if the burden of creating such a system outweighs its benefits.⁴⁹ FDA also may waive the requirement if an aspect of the ETASU for the RLD is protected by one or more patents or is a trade secret, and the ANDA applicant certifies that it unsuccessfully sought to license the protected aspects of the ETASU.⁵⁰

⁴² Section 505-1(f)(1) of the FD&C Act.

⁴³ Id.

⁴⁴ Section 505-1(f)(8) of the FD&C Act.

⁴⁵ Section 909(b)(1) of FDAAA; 21 CFR 314.520 describes “restrictions” to assure safe use, while FDAAA refers to “elements” to assure safe use.

⁴⁶ 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, 73 FR 16313-16314 (March 27, 2008).

⁴⁷ FDAAA, section 909(b)(3).

⁴⁸ Section 505-1(i)(1) of the FD&C Act.

⁴⁹ Id.

⁵⁰ Id.

II. DISCUSSION

A. Initial ANDA Submissions

You maintain that the specific elements of the Xyrem Success Program constitute labeling and/or conditions of use.⁵¹ You further maintain that if an initial ANDA submission referencing XYREM does not contain information sufficient to demonstrate that the proposed drug product would have the same labeling and conditions of use as XYREM in the form of a “substantially complete risk management proposal” with all the elements you identify as labeling and/or conditions of use, the ANDA should not be accepted for review, reviewed, or approved by FDA. We disagree.

As an initial matter, the specific issue raised by your assertions is what an ANDA submission referencing an RLD subject to a deemed REMS or an approved REMS must include to be received for filing by FDA. In your petition, you maintain that aspects of the XYREM Success Program constitute labeling.⁵² Although we agree that certain aspects of the XYREM Success Program constitute part of the labeling for Xyrem, and so stated in the approval letter for the sNDA, for the reasons described below, we do not require an ANDA to contain all of this information to be received for review. Nor do we require, to receive an ANDA for review, those elements of Xyrem Success Program that you assert constitute conditions of use.

For the purposes of this response only, we assume *arguendo* that all the items you identify as labeling and/or conditions of use are such items. The question then becomes whether an ANDA referencing Xyrem must contain all of these items to be received for review. Before reaching the substance of your claims, FDA notes that your position that FDA *must* refuse to receive an ANDA if it lacks information demonstrating that it has the same labeling or conditions of use as the RLD is based on a flawed premise. As described above, FDA conducts an initial review of an ANDA to determine whether, as a threshold matter, the application is sufficiently complete for FDA to receive it for review.⁵³ Citing 21 CFR 314.101, you assert that FDA “*may not* receive an ANDA” unless it contains a proposed risk management system with same elements as the Xyrem success program.⁵⁴ None of the circumstances in which the Agency must refuse to file an ANDA apply to the present situation, however.⁵⁵ The particular provision you cite -- circumstances in which FDA “*may*” refuse to receive or file an application where “it is incomplete because it does not on its face contain information required under section 505(b), section 505(j), or section 507 of the Act and 314.50 or 314.94” -- is discretionary. Accordingly, if an ANDA lacks any information required for approval, FDA may refuse to receive the application for review, but it is entirely within the Agency’s discretion as to whether it will refuse to receive an ANDA for review on these grounds.⁵⁶ If FDA

⁵¹ Petition, at 11-13.

⁵² Petition, at 10-12.

⁵³ 21 CFR 314.101(b).

⁵⁴ Petition, at 9 (emphasis added).

⁵⁵ 21 CFR 314.101(e).

⁵⁶ 21 CFR 314.101(d)(3).

determines that an ANDA is sufficiently complete to permit a substantive review, the application will be received and reviewed.

The appropriate question, therefore, is whether FDA, pursuant to its discretion under 21 CFR 314.101(d)(3), should require all of the risk management system items you cite at ANDA filing to be received for review. For the reasons set out below, FDA declines to adopt your position, because it would be inconsistent with the process set forth in section 505-1(i) of the FD&C Act to address generic products that reference an RLD with a REMS, as well as elements of section 505(j) and FDA's regulations.

As described above, a REMS approved under an ANDA is only required to have certain elements (a Medication Guide or patient package insert and ETASU) if the RLD REMS contains these elements.. If an RLD with a REMS has a Medication Guide or patient package insert, FDA generally requires an ANDA to contain such material to receive the application for review. However, FDA generally does not require initial ANDA submissions to include substantially complete ETASU, because the ANDA applicant and the holder of the approved NDA for the RLD are required under the FD&C Act to utilize a single, shared system (unless the agency waives the requirement), and that single, shared system must be negotiated by the RLD sponsor and the ANDA applicant before it can be submitted and approved.⁵⁷

It would not be reasonable to require an ANDA applicant to enter into negotiations regarding ETASU with an RLD sponsor before the applicant first submits an ANDA for several reasons. First, such a requirement would risk the expenditure of resources by the ANDA and RLD sponsors regarding a single, shared system prior to the Agency's determination that the ANDA otherwise is acceptable for review.

Second, requiring ETASU for a generic product to be resolved prior to submission, to the extent that it would delay generic approval, would be inconsistent with the policy embodied in section 505-1(f)(8) of the FD&C Act, which prohibits the holder of an approved application from using ETASU required by FDA to block or delay approval of an ANDA. FDA notes that the only party that would gain from requiring the collaboration contemplated in section 505-1(i)(1)(B) prior to ANDA submission is an RLD sponsor, which would benefit from the likely resulting delay of submission, receipt for review, and if the applicable statutory requirements are met, approval of a generic product. Permitting the collaborative process to proceed concurrently with FDA's substantive review of the ANDA, on the other hand, is more likely to result in expedient approval of generic products while ensuring that sufficient protections are in place to assure safe use of such products as required under section 505-1(i).

Third, requiring the submission of the ETASU at the time the ANDA is submitted would be inefficient because it likely would result in at least two submissions of the ETASU, one in response to REMS notification, and another after the negotiations conclude, and two agency reviews of the proposed REMS.

⁵⁷ Section 505-1(i) of the FD&C Act.

For these reasons, after receiving for review an ANDA referencing an RLD subject to an approved REMS, FDA generally will notify the ANDA applicant that a REMS is necessary for its product under section 505-1(i), and will identify the minimum aspects of the RLD's approved REMS that are required for approval of the proposed generic drug. FDA also will instruct the ANDA applicant to work with the NDA holder to create such a single, shared system for ETASU to fulfill the statutory requirement.

For an ANDA referencing an RLD for which the final REMS has not been approved, FDA does not require the ANDA applicant to include at filing those elements of the deemed REMS that constitute ETASU. This is because, as Congress directed, any ETASU in a deemed REMS will be replaced by the ETASU in an approved REMS.⁵⁸ The only part of a deemed REMS that the Agency requires at filing is a Medication Guide or patient package insert, because those are part of labeling that are required to be the same as the RLD. FDA directs the ANDA applicant to work with the NDA holder to create a single, shared system to implement the ETASU that will be approved as a final REMS, as required by section 505-1(i)(1). If, over the course of the ANDA review, FDA determines that such an ANDA may be ready for approval before final approval of the REMS, FDA will direct the ANDA applicant to submit a proposed risk management plan with ETASU that are comparable to the ETASU that are approved for the RLD to have adequate risk management elements in place for the ANDA until the final REMS is approved.⁵⁹

For the foregoing reasons, the Agency will not refuse to file an ANDA on the ground that it does not contain, as you describe, "a substantially complete proposed risk management system," as part of its initial submission. Your request that the Agency refuse to accept for review, review, or approve ANDAs referencing XYREM that do not contain a substantially complete proposed risk management system as part of the initial ANDA submission is denied.

B. FDA's Treatment of ANDAs Referencing XYREM

⁵⁸ Sections 909(b)(1) and (3) of FDAAA.

⁵⁹ FDA notes that section 909(b)(1) of FDAAA provides that "[a] drug that was approved before the effective date of this Act is, in accordance with paragraph (2), deemed to have in effect an approved risk evaluation and mitigation strategy under section 505-1 [...] if there are in effect on the effective date of this Act elements to assure safe use required (A) under section 314.520 or section 601.42 of title 21, Code of Federal Regulations; or (B) otherwise agreed to by the applicant and the Secretary for such drug" (Section 909(b)(1) of FDAAA). It has been FDA's experience that in the post-market setting, long delays may ensue between when a proposed REMS is submitted and when it is approved because sponsors of drugs with deemed REMS have little incentive to work with the FDA to come to agreement on the specific terms of the REMS quickly and, indeed, have incentives to delay approval of the REMS so that they can continue to operate under the risk management plan previously approved. FDA has determined that under these circumstances, it would be unreasonable to interpret section 505-1(i)(1) to require a single, shared system for a deemed REMS because experience shows that the deemed REMS is likely to change before it is approved, particularly when lengthy delays ensue before approval. Such an interpretation effectively would require ANDA applicants and RLD sponsors to negotiate twice – once to develop a single, shared system to implement the ETASU in the deemed REMS (that will be replaced by the final approved REMS), and then again to implement the ETASU that will be part of the approved REMS. This would effectively delay the approval of the generic drugs, and there is no evidence that Congress intended such an outcome.

1. *Request to Rescind Roxane's ANDA*

You maintain that FDA's previous acceptance of Roxane's ANDA referencing XYREM, which you assert lacked sufficient information as initially submitted to demonstrate that the proposed drug product contained a substantially complete risk management system proposal, should be rescinded, and that FDA should require the applicant to resubmit a new ANDA that includes what you view as the necessary information.⁶⁰ You also maintain that Roxane circumvented the regulatory requirements for ANDA applicants by submitting an incomplete ANDA, and if FDA does not rescind Roxane's ANDA, future ANDA applicants will be encouraged to also circumvent regulatory requirements.⁶¹ For the reasons set forth above, we disagree with these assertions and decline your request. As previously discussed, the regulations allow FDA discretion when determining whether an ANDA has met the requirements for receipt for review. FDA determined that Roxane's ANDA was sufficiently complete to permit substantive review, and received it for review.

2. *Subsequent Submissions for Roxane's ANDA*

You assert that Roxane's ANDA was incomplete when initially filed because it did not contain a substantially complete proposed risk management system, and subsequent submissions should not be allowed to remedy this initial deficiency.⁶² We disagree. As discussed above, within the discretion granted the Agency, FDA determined that Roxane's initial ANDA submission was sufficiently complete to permit substantive review, and FDA received it for review.

Again, FDA expects ANDA applications referencing XYREM to submit a Medication Guide with initial ANDA submissions, but does not expect initial submissions to include proposed ETASU. FDA expects ANDA applicants referencing XYREM to submit proposed ETASU after working with Jazz to create a single, shared system of ETASU, and after seeking a license for any aspects of XYREM's ETASU that are protected intellectual property.

3. *Future ANDAs*

You assert that in the future FDA should not accept any ANDA that references XYREM unless the initial ANDA submission contains information sufficient to demonstrate that the proposed drug product would have a substantially complete risk management system proposal.⁶³ For all of the reasons set forth above, this request is denied. FDA will review each initial ANDA submission referencing XYREM to determine whether it is sufficiently complete to permit substantive review. The Agency will make filing decisions based on the contents of the individual applications submitted.

⁶⁰ Petition, at 16.

⁶¹ Petition, at 14.

⁶² Petition, at 16-17.

⁶³ Petition, at 16.

C. FDA's Role Within the Hatch-Waxman Framework

1. *Gate-Keeping Function*

You maintain that FDA's refusal to file an incomplete ANDA constitutes a gate-keeping function that prevents the initiation of premature patent infringement litigation by ensuring that all elements of an ANDA that implicate patents listed for the RLD are sufficiently complete to enable judicial review.⁶⁴ This assertion is unfounded.

FDA reviews an ANDA to determine whether the proposed generic drug product meets the statutory and regulatory requirements for marketing approval.⁶⁵ As described above, FDA's involvement with respect to patent listing, patent certifications and related notices of invalidity and/or non-infringement, and any resulting patent litigation, is limited to a ministerial function. To the extent that an RLD sponsor or patent holder thinks that a notice of invalidity or non-infringement was insufficient, FDA's regulations recognize a limited relief available from the agency under 21 CFR 314.95(c) and (f). It is not FDA's role to consider any impact that the receipt and review of an ANDA by FDA may have on patent litigation.

2. *Prejudice to Jazz*

You maintain that FDA's acceptance of Roxane's ANDA for review was inconsistent with the Hatch-Waxman Amendments and prejudiced Jazz because it forced the company to initiate patent infringement litigation that was not ripe for judicial review, and caused the 30-month stay to begin prematurely, due to the fact that the material that might potentially infringe Jazz's XYREM Success Program patents—Roxane's proposed risk management system—had not been submitted to the FDA when Jazz was required to initiate the lawsuit. These assertions are unfounded.

As discussed above, the Agency has a limited role with respect to patents for RLDs and patent litigation triggered by ANDA filings. FDA does not consider in its "receipt for review" analysis the potential impact receipt of an ANDA may have in related patent litigation.

Moreover, Jazz is prohibited from using an ETASU required by FDA to block or delay approval of an ANDA referencing XYREM.⁶⁶ Requiring initial ANDA submissions to include a substantially complete proposed risk management system would necessitate submission of a second, revised proposed risk management system after the process of working towards a single, shared system is complete. Such a duplicative submission requirement at Jazz's request would almost certainly delay approval of an ANDA referencing XYREM, contrary to the mandates of the FD&C Act.

⁶⁴ Petition, at 14.

⁶⁵ Section 505(j)(2)(A) and (j)(4) of the FD&C Act and 21 CFR 314.94(a).

⁶⁶ Section 505-1(f)(8) of the FD&C Act.

You further maintain that Jazz will be significantly prejudiced if Roxane's ANDA is approved with a REMS that differs materially from its currently proposed risk management system, but that nevertheless infringes Jazz's patents, because Jazz will have to initiate a second patent infringement lawsuit without the benefit of a 30-month stay, and possibly when an infringing product is already on the market. Again, FDA's involvement with respect to patents, patent certifications, and patent litigation is limited. Even without the 30-month stay, Roxane would run the risk of marketing an infringing product if it marketed its generic product prior to resolving the patent issues.

3. *Prejudice to Other ANDA Applicants*

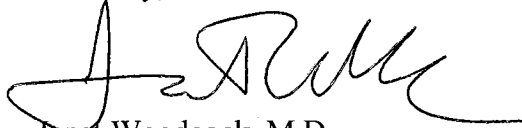
You maintain that FDA's "premature" acceptance of Roxane's "incomplete" ANDA prejudiced other ANDA applicants that may have been expending significant resources to develop a proposed risk management system before submitting their ANDAs. This assertion is without merit.

FDA will receive ANDAs referencing XYREM for review that are sufficiently complete to permit substantive review, as discussed at length above. Because Roxane met this standard, FDA received its ANDA for review. The Agency will receive other ANDAs referencing XYREM for review that also meet this standard. We disagree with the proposition that receipt of Roxane's ANDA for review serves to prejudice other ANDA applicants, because all ANDA applicants must meet the requirements for receipt and approval.

III. CONCLUSION

For the reasons explained in this response, your petition is denied.

Sincerely,

A handwritten signature in black ink, appearing to read "J. Woodcock", with a long horizontal flourish extending to the right.

Janet Woodcock, M.D.

Director

Center for Drug Evaluation and Research