Boehringer Ingelheim
Roxane Laboratories

December 6, 2012

VIA REGULATIONS.GOV

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

RE: FDA-2012-P-0733: ANDAs Referencing Xyrem® (sodium oxybate) Oral Solution, Including an Abbreviated New Drug Application (ANDA) Submitted by Roxane Laboratories, Inc. on July 8, 2010.

Over two years ago, FDA accepted for filing Roxane Laboratories, Inc.'s ("Roxane") ANDA referencing Xyrem® (sodium oxybate) oral solution, designating it "substantially complete" and thus suitable for FDA review. Since that time, Xyrem®'s sponsor (Jazz Pharmaceuticals, Inc. ("Jazz")) repeatedly has sought to thwart generic competition for this important drug product by serially filing Citizen Petitions that seek to undermine FDA's review of Roxane's pending ANDA. In its first Citizen Petition (Docket No. 2012-P-0499), Jazz reprised long-discredited legal claims regarding FDA's obligation to publish bioequivalence requirements prior to accepting an ANDA for filing, and advanced scientifically dubious claims that the Agency rightly rejected as both "unsupported" and "unpersuasive." Letter from J. Woodcock to P. Honerkamp, FDA-2012-P-0499, at 18 (Nov. 13, 2012).

Having once tried and failed to thwart FDA's acceptance of Roxane's ANDA, Jazz now tries again with this second Citizen Petition (FDA Docket No. 2012-P-0733). It requests that FDA (1) rescind its acceptance of any previously-filed ANDA referencing Xyrem®, including Roxane's, if the initial ANDA submission did not contain a proposed system of risk evaluation and mitigation strategies ("REMS") that precisely mirrors Xyrem®'s allegedly patent-protected drug distribution program, which FDA has deemed equivalent to a REMS though the program has never formally been approved as a REMS; (2) not accept for review any ANDA referencing Xyrem® that does not propose a REMS that mirrors Jazz's drug distribution program; and (3) require previously submitted ANDAs to be resubmitted with proposed mirror-image REMS and indeed provide Jazz with a new thirty-month stay.

Those requests are even more desperate than the "unsupported" and "unpersuasive" claims Jazz advanced in its last Citizen Petition—which likely explains why Jazz did not bother advancing those claims in its opening gambit to thwart generic competition. Jazz's basic claim is that any ANDA submission for which the reference listed drug ("RLD") has a REMS or REMS-

like program such as Xyrem®'s must include—on the date of initial submission to FDA—both an exhaustive description of the ANDA's proposed REMS and the full panoply of REMS-related materials utilized by the RLD holder, because REMS materials are a form of product "labeling" and reflect "conditions of use" that must be "the same as" the RLD's. 21 U.S.C. §§ 355(j)(2)(A)(i), (v). Because Roxane's ANDA allegedly lacked some of these materials, Jazz now asks FDA to rescind acceptance of Roxane's ANDA and restart Jazz's 30-month stay upon the re-submission of an ANDA that contains those materials. Those claims are baseless for three principal reasons.

First, the whole premise of Jazz's argument is wrong. Whatever arguable merit there may be to Jazz's claim that Xyrem®'s REMS-like program includes materials that fall within the ***general*** definition of "labeling" (21 U.S.C. § 321(m)) and thus are subject to Hatch-Waxman's ***general*** sameness requirement (21 U.S.C. § 355(j)(2)(A)), the key point here is that an ANDA applicant's REMS-related obligations are ***specifically*** defined by the ***REMS-specific*** statute at 21 U.S.C. § 355-1(i). That law makes clear that ANDA applicants must replicate ***only*** the RLD's REMS-related "Medication Guide or patient package insert," 21 U.S.C. § 355-1(i)(1)(A), and ***expressly*** contemplates that the ANDA applicant and FDA will settle details of the generic REMS program ***after*** the ANDA is submitted. Indeed, the statute specifically contemplates that ANDAs may employ "***different*** … elements to assure safe use" ("ETASU") than the RLD. *Id.* § 355-1(i)(1)(B) (emphasis added). It thus is no surprise that FDA has never adopted Jazz's construction, which cannot be squared with the plain language of 21 U.S.C. § 355-1(i).

Second, Jazz still would not be entitled to its requested relief even if FDA were to accept Jazz's claim that initial ANDA submissions should include all conceivable REMS-related materials. Initial ANDA submissions are evaluated only for "substantial completeness," which is a modest standard under which FDA assesses only whether the submission is deficient "on its face." By any measure, Roxane's ANDA met that standard—which explains why FDA accepted it in the first place. Accordingly, even if FDA were to embrace Jazz's remarkable contention that mirror-image REMS materials should be included with every initial ANDA submission (which often is impossible due to the confidential or otherwise undisclosed nature of many REMS-related documents), the Agency would not have to reject Roxane's ANDA, much less do so retroactively. Instead, FDA has ample discretion to permit Roxane to supplement its ANDA.

Finally, even if there were merit to Jazz's substantive arguments, its request for a new 30-month stay is outrageous. Although the Citizen Petition fails to disclose it, Jazz already argued in its patent case against Roxane that Roxane's allegedly untimely disclosure of its proposed REMS program prejudiced Jazz's ability to fairly litigate its claims—and accepted a ***less-than-three-week*** extension of the briefing schedule to resolve that issue. Suffice it to say, that resolution fatally undermines Jazz's remarkable assertion here that it now needs ***another 30 months*** to protect its interests. Nothing in Hatch-Waxman entitles Jazz to such a windfall.

The petition should be denied.

ARGUMENT

I. Roxane's ANDA Contained All Information Required For An Initial Submission.

Jazz spills considerable ink detailing the alleged labeling deficiencies in Roxane's ANDA, but never addresses the fact that Roxane's ANDA contained draft product labels and complete patient package inserts, a draft Medication Guide, and a side-by-side comparison of these elements to Xyrem®'s. These are the ***only*** labeling elements FDA has ever required ANDA applicants to include with an initial ANDA submission, and they are the ***only*** labeling elements FDA specifically designates as being subject to the "sameness" requirement for an initial ANDA submission. *See* 21 C.F.R. § 314.94(a)(8)(iv) ("Labeling (including ***the container label, package insert, and, if applicable, Medication Guide***) proposed for the [ANDA] product must be the same as the labeling approved for the [RLD], except for [permitted] differences.") (emphasis added).[1]

Ignoring the text of FDA's regulations and the abundant materials provided by Roxane in its ANDA, Jazz instead claims that Roxane was obligated to do more because Xyrem® is allegedly subject to a REMS-like program ("the Xyrem® Success Program") pursuant to which Jazz distributes various written materials, including an informational booklet, physician enrollment forms, and a video for patients. According to Jazz, these materials meet the general definition of "labeling"[2] under 21 U.S.C. § 321(m); therefore are subject to the general sameness requirement set forth at 21 U.S.C. § 355(j)(2)(A); and thus should have been included in Roxane's original ANDA submission. Pet. at 10-12.

That proposition is particularly far-fetched here, since—in contrast to the labeling elements FDA specifically requires ANDAs to include—Jazz's REMS-like materials have never formally been approved as a REMS, Xyrem® does not appear on FDA's official list of products that are subject to an approved REMS, and Xyrem®'s REMS-like materials thus have never been available from FDA for Roxane to review and replicate (much less do so at the time of Roxane's original ANDA submission). *See* FDA, Approved Risk Evaluation and Mitigation Strategies (REMS), *available at* http://tinyurl.com/OfficialREMSList (last visited Dec. 5, 2012).[3] More fundamentally, the whole premise for Jazz's labeling argument is incorrect. Whether or

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[1] These limitations make sense. Obligating ANDA applicants to replicate every conceivable piece of "labeling" at the time of submission would require generic applicants to copy and submit direct-to-consumer advertising and even promotional website mockups—communications that fall within the general definition of "labeling," but which have no applicability to ANDA products and which FDA has never required ANDA applicants to produce (much less submit at the time of filing).

[2] Jazz also asserts in passing that certain aspects of its REMS-like program constitute "conditions of use" that likewise are subject to the sameness requirement. Pet. at 12-13. That assertion is frivolous even on its own terms. FDA has defined "conditions of use" as "encompass[ing] how, to whom, and for which purpose a drug is used." *See Viropharma, Inc. v. Hamburg*, __ F. Supp. 2d __, 2012 WL 1388183, *15 n. 24 (D.D.C. Apr. 23, 2012) (quoting FDA). The "how" does not entail the mechanics of distribution under a REMS program: it involves the dosing regimen for the product. The "whom" is not a list of intermediaries who distribute the product under a REMS program; it is the patient population that needs treatment with the product. And the "purpose" has nothing whatsoever to do with REMS; it is about the indications for which the drug is prescribed. Those things are covered by the product's package insert and labeling, not the details of a REMS.

[3] Nor is this case unique. NDA holders commonly refuse to provide REMS-related materials to ANDA applicants even after FDA has accepted an ANDA for review.

not certain components of the Xyrem® Success Program could be construed to fall within the statute's ***general*** definition of "labeling" under 21 U.S.C. § 321(m), an ANDA applicant's REMS-related obligations are ***specifically*** enumerated elsewhere in Hatch-Waxman—the ***REMS-specific*** statute codified at 21 U.S.C. § 355-1(i). It is axiomatic "that the specific governs the general," *Morales v. Trans World Airlines, Inc.*, 504 U.S. 374, 384 (1992), and the Supreme Court thus long ago declared that "[g]eneral language of a statutory provision, although broad enough to include it, will not be held to apply to a matter specifically dealt with in another part of the same enactment." *D. Ginsberg & Sons v. Popkin*, 285 U.S. 204, 208 (1932).

That matters here, because the REMS statute specifically provides that ANDA applicants do ***not*** need to replicate every element of the RLD holder's REMS program. Instead, it provides that ***only*** the product's "Medication Guide or patient package insert, if required under subsection (e) of this section for the applicable listed drug," must be provided by ANDA applicants in every case. 21 U.S.C. § 355-1(i)(1)(A). As noted above, Roxane's ANDA included these elements. Beyond those two components, however, the REMS statute makes clear that ANDAs must make provision ***only*** for REMS-related "[e]lements to assure safe use, if required under subsection (f) for the listed drug." *Id.* § 355-1(i)(1)(B).

That is notable for two reasons. First, the fact generic applicants must only include those ETASU "***under subsection (f)***" is critical, because many of the items Jazz claims Roxane's initial ANDA submission was missing do not fall within subsection (f). *See id.* § 355-1(f)(3) (ETASU include provider certification requirements, pharmacy certification requirements, distribution restrictions, patient registries, and patient monitoring). Jazz's physician informational booklet, patient informational booklet, patient video, and patient and doctor letters are not ETASU under subsection (f); instead, they are either "additional elements" or part of a "communication plan" under 21 U.S.C. § 355-1(e). Under the plain language of 21 U.S.C. § 355-1(i)(1)(B), ANDA applicants are not required to mimic those aspects of the RLD's REMS program (or Xyrem®'s REMS-like program)—whether at the time of submission or thereafter.

Second, and even with respect to those items that do fall under subsection (f), the statute expressly contemplates that the ANDA applicant, NDA holder, and FDA will collaborate ***after an ANDA is submitted*** to determine how the subsection (f) REMS elements for ANDA products will function in relation to the RLD's subsection (f) elements. Thus, while the statute contemplates the possibility of having ANDA and NDA holders "share" a system of subsection (f) elements—a possibility that even by its own terms would not necessarily require ANDA applicants to mimic every word the brand manufacturer uses in connection with the implementation of, for instance, a patient registry (much less that it (A) commit to doing so before submitting an ANDA and (B) include reference to such a commitment in its initial ANDA submission)—the statute goes on to authorize ***separate and distinct*** subsection (f) programs for ANDA applicants if "the burden of creating a single, shared system outweighs the benefit of a single, [shared] system." *Id.* § 355-1(i)(1)(B)(i). Indeed, the statute even authorizes ANDA applicants "to use ***a different***, comparable aspect of the elements to assure safe use." *Id.* § 355-1(i)(1)(B) (emphasis added).

These provisions of the REMS statute fatally undermine Jazz's claims. On one hand, these provisions demonstrate that the content of a REMS program for an ANDA product is not

fixed *a priori*. Any consideration of waiving of the statutory preference for a shared system necessarily occurs ***after*** an ANDA is submitted. *Id.* § 355-1(i)(1)(B)(i) ("The Secretary may waive the requirement under the preceding sentence for a drug ***that is the subject of an abbreviated new drug application*** ... taking into consideration ***the impact on ... the applicant for the abbreviated new drug application***.") (emphasis added). And where patents are implicated, the statute further authorizes FDA to act as an intermediary in negotiating ***post-ANDA submission*** agreements between the NDA holder and ANDA filer regarding the subsection (f) elements that will apply to ANDA products. 21 U.S.C. § 355-1(i)(1)(B)(ii). Because the statute thus expressly contemplates that the scope of an ANDA applicant's subsection (f) REMS obligations will not be settled until ***after*** its submission of an ANDA, it makes no sense to insist (as Jazz does) that an ANDA applicant somehow is obligated to commit to mimicking the brand manufacturer's REMS program in its entirety ***before*** FDA can even accept an ANDA for review.

On the other hand, the fact that these provisions of the REMS statute expressly authorize generic applicants to use "different" subsection (f) elements forecloses Jazz's assertion that REMS components which qualify as "labeling" are subject to Hatch-Waxman's general sameness requirement. Were that so, the statute would be at war with itself—labeling would have to be both the same and different. That makes no sense, and again, the venerable rule that the specific governs the general solves this problem.

At the end of the day, the REMS-specific statute for ANDAs that is codified at 21 U.S.C. § 355-1(i) establishes an iterative process that necessarily follows initial ANDA submission and which cannot be squared with Jazz's effort to shoehorn REMS and REMS-like programs into Hatch-Waxman's general rules for up-front labeling sameness. Under the REMS statute, and outside the statute's fixed requirement that ANDAs replicate the RLD's Medication Guide and patient package insert (as Roxane did here), FDA's consistent practice has been to inform ANDA filers which ETASU the Agency believes are necessary after accepting an ANDA for filing; encourage the ANDA applicant and NDA holder to negotiate a workable system; intercede in the event those negotiations break down; and when—and only when—those issues are finally resolved, require the ANDA filer to submit detailed REMS materials as a supplement to the already-filed ANDA.

This established practice is entirely consistent with 21 U.S.C. § 355-1(i). And it makes sense. Again, even if the ANDA filer ultimately is required to use forms and other written REMS-related materials that largely mirror those used by the NDA holder, the composition of these materials is entirely dependent upon the post-filing course of events that the statute sets in motion. Requiring ANDA applicants to commit—in exhaustive detail—to a course of conduct before the Agency can even accept its ANDA is thus hopelessly impractical. Jazz's contention that FDA cannot accept an ANDA for filing unless and until the applicant submits a complete REMS that mirrors every last detail of the NDA holder's pre-ANDA REMS or REMS-like program is frivolous.

II. At The Very Least, Roxane's ANDA Was Substantially Complete—And There Is No Colorable Basis For Rescinding FDA's Years-Old Acceptance Of Roxane's ANDA Now.

Even if Jazz were correct that Roxane's ANDA should have contained any and all REMS-related written materials from the outset (despite the fact that Jazz's materials have never been made publicly available and indeed have never been formally approved as a REMS), FDA still would not be required to "rescind the acceptance" of Roxane's ANDA. Pet. at 1. Simply put, no statute or regulation requires the Agency to retroactively rescind its years-old acceptance of Roxane's ANDA—least of all that it must do so after adopting an unprecedented and indeed game-changing interpretation of the requirements for submitting ANDAs that reference RLDs which are subject to REMS. Jazz's request thus must be denied even if the Agency accepts the underlying legal premise for Jazz's argument.

Jazz's argument on this score is frayed at both ends. As a threshold matter, Jazz is wrong that Roxane's ANDA was not "substantially complete" at the time it was filed. FDA reviewed Roxane's ANDA at the time of submission and found it to be substantially complete, issuing an accepted for filing notice. And as Jazz itself concedes, the standard FDA properly applied in making that determination is easily satisfied: It requires only that the ANDA "is sufficiently complete to permit a substantive review," Pet. at 9 (quoting 21 C.F.R. § 314.101(b)(1), and as FDA's regulations long ago made clear, an ANDA fails that modest test only if "it does not ***on its face*** contain information required." *Id.* (emphasis added; quoting 21 C.F.R. § 314.101(d)); *see also* FDA, *New Drug Evaluation Guidance Document: Refuse to File* (1993) ("Refusal to file an application ... is, in general, based on omissions or inadequacies ***so severe as to render the application incomplete on its face.***") (emphasis added).

Jazz's argument is entirely inconsistent with that standard. Though it pays lip service to the standard, Jazz does ***not*** actually allege that Roxane's initial ANDA submission failed ***on its face*** to include proposed labeling with its initial ANDA submission. Instead, Jazz argues that ***a detailed substantive comparison*** between the voluminous labeling Roxane proposed to include with its ANDA product and the alleged "labeling" included as part of Jazz's Xyrem® Success Program (but never made publicly available) would have revealed gaps in Roxane's proposed labeling (assuming *arguendo* that Jazz is correct that the content of Roxane's REMS-related submissions is governed by the general labeling requirements rather than the REMS-specific provisions of the statute). Suffice it to say, that profoundly substantive approach—which would require FDA to begin each ANDA intake process by reviewing the brand manufacturer's product approval word-by-word; applying the statute and Agency regulations to define the scope of the brand manufacturer's "labeling" on a case-by-case basis; and then engaging in a word-by-word comparison of the ANDA's proposed labeling to the NDA holder's to ensure no word is missing—would make a mockery of the "substantially complete" standard, which is intended only to ensure that the applicant has made a "good faith effort to meet the [statutory] requirements." H. Rept. 98-857, Part 1 at 24, 98th Cong. 2d Sess. (June 21, 1984).

Even if there were some basis for that approach at the threshold, however, there is no basis for Jazz's requested remedy. The statute requires FDA to deny approval of an ANDA if the submission ***ultimately*** is found not to contain the required statutory elements, 21 U.S.C. § 355(j)(4), but provides no comparable authority for the Agency (much less obligate it) to

retroactively rescind its receipt of an ANDA for review where FDA later determines in a contested adjudicatory proceeding that certain information should have been included with the original application. The only authority for anything approaching such a remedy comes from the Agency's implementing regulations, and even then, the authority granted is discretionary. *See* 21 C.F.R. § 314.101(d) (providing that FDA "may" refuse to file an ANDA or "may" consider an ANDA to not be received if the ANDA is incomplete). Indeed, FDA's regulations go on to provide procedural protections for ANDA applicants in such cases, *id.* § 314.101(a)(1)(3), and make clear that FDA timely should provide applicants with an opportunity to correct the deficiencies. 21 C.F.R. § 314.101(b)(3)(ii); *see also id.* at § 314.101(a)(1) (requiring FDA to make its filing determination within 60 days of receiving an ANDA). In short, Jazz is dead wrong that FDA's longstanding receipt of an ANDA categorically must be rescinded if the Agency years later determines that the submission was missing some required information—and is on even shakier footing in asserting that "subsequent submissions cannot 'cure' an ANDA that was deficient ... when initially filed." Pet. at 16-17.

Finally, Jazz's requested relief is particularly inappropriate here. FDA accepted Roxane's ANDA for filing more than two years ago, and Roxane (consistent with the iterative process for the development of generic REMS programs set forth in 21 U.S.C. § 355-1(i)) has been working cooperatively with FDA to develop a suitable REMS program for ANDAs referencing Xyrem®. Under these circumstances, Jazz's request that FDA rescind its years-old acceptance of Roxane's ANDA is baseless.

III. FDA Should Reject Jazz's Eleventh-Hour Request For A Windfall.

Lastly, FDA should reject Jazz's outlandish request that the Agency not only rescind its years-old acceptance of Jazz's ANDA for filing but subject any resubmitted ANDA to a new thirty-month stay. Jazz's basic argument here is that FDA's decision to accept Roxane's ANDA was "fundamentally inconsistent" with Hatch-Waxman, which "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." Pet. at 13-14.

Whatever merit that assessment of the statute may have, it does not remotely justify Jazz's demand for a new thirty-month stay. As the statute required, Roxane timely notified Jazz that FDA had accepted its ANDA for filing and provided a detailed statement explaining Roxane's non-infringement position. Jazz promptly sued Roxane in federal court, and after receiving Roxane's ANDA in discovery, had no difficulty formulating infringement contentions despite the alleged lack of detail in Roxane's original ANDA submission. Indeed, Jazz did not complain about the sufficiency of Roxane's disclosures until late 2011, when it complained that it needed additional time to prepare its *Markman* claim-construction brief based on additional disclosures relating to Roxane's proposed REMS program.[4] The parties amicably resolved that dispute, and Jazz agreed to accept a ***less-than-three-week*** extension to amend its infringement contentions and file its *Markman* brief.[5] It remains a mystery how Jazz thinks it credibly can

[4] Letter from C. Lizza to Hon. C. Waldor, *Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*, No. 10-6108, at 2 (Dec. 20, 2011).

[5] *See* Feb. 2, 2012 Order, *id.*

argue here that Roxane's allegedly untimely disclosures "effectively frustrated the ripening of the dispute for at least a year" and so disrupted the patent case that a new ***30-month*** stay is necessary, Pet. at 15, when it was content to accept a ***less-than-three-week*** extension of a briefing deadline in the district court; Jazz's petition does not even acknowledge those events, much less attempt to explain them.

Nor is there any merit to Jazz's suggestion that other potential ANDA applicants have been prejudiced. Pet. at 15-16. If other ANDA applicants feel that Roxane has done them wrong, they can file citizen petitions of their own. But none has—and the fact that brand manufacturer Jazz finds itself forced to shed crocodile tears on behalf of its would-be generic competitors speaks volumes.

Finally, there is no merit to Jazz's suggestion that Roxane pulled a "bait-and-switch," Pet. at 15, that is comparable to the kind of "sham ANDA" that would warrant a new 30-month stay. Pet. at 14 (citing FDA, *Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions; Final Rule*, 59 Fed. Reg. 50,338, 50,349 (Oct. 3, 1994)). That is nonsense. As Roxane already has explained, there is no legitimate basis for rescinding the acceptance of Roxane's ANDA at this late date based on the adoption of an unprecedented and expectation-shattering interpretation of the regulatory requirements in the context of a disputed adjudicatory proceeding. If nothing else, Roxane reasonably interpreted the statute as creating an iterative process between the generic applicant and FDA regarding ANDAs referencing NDAs that are subject to REMS; and FDA itself obviously shared that eminently reasonable view of the statute, because it accepted Roxane's ANDA for filing more than two years ago.

Contrary to Jazz's assertion that "[r]escinding 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," the remedy Jazz seeks flies in the face of basic principles of equity. Even if FDA erred when it accepted Roxane's ANDA in September 2010 (and FDA did not), the fact remains that FDA did accept the ANDA and Roxane has acted in reliance on that decision for more than two years. If FDA had determined at the outset that Roxane's ANDA was incomplete, it would have been obligated to timely notify Roxane of that determination and provide Roxane with the procedural protections afforded by law. *See, e.g.*, 21 C.F.R. §§ 314.101(a)(1), (b)(3). And Roxane would have worked promptly to provide FDA with whatever additional materials FDA determined were necessary. There simply is no basis to strip Roxane of those protections and that opportunity—much less to force countless consumers to continue paying monopoly prices for Xyrem®—so that Jazz can reap an undeserved windfall.

CONCLUSION

The petition should be denied for the foregoing reasons.

Sincerely,

Randall S. Wilson
Vice President, Scientific, Medical and Regulatory Affairs
Roxane Laboratories, Inc.

VERIFICATION

I certify that, to my best knowledge and belief: (a) I have not intentionally delayed submission of this document or its contents; and (b) the information upon which I have based the action requested herein first became known to me on or about July 10, 2012-present. 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: Roxane Laboratories, Inc., in the ordinary course of my employment. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.