October 24, 2012

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

RE: FDA-2012-P-0499: Approval Requirements for ANDAs Referencing Xyrem® (sodium oxybate) Oral Solution

On May 18, 2012, Jazz Pharmaceuticals, Inc. ("Jazz") submitted the above-referenced Citizen Petition requesting that FDA not accept, review, or approve any ANDA referencing Xyrem® (sodium oxybate) oral solution until the Agency publishes in the Orange Book bioequivalence requirements for such ANDAs, and urging FDA to immediately publish bioequivalence requirements for such ANDAs that in certain circumstances would require the submission of various *in vivo* bioequivalence studies. Roxane Laboratories, Inc. ("Roxane") has a direct interest in the subject matter of the Jazz Citizen Petition because it submitted (and FDA accepted) an ANDA referencing Xyrem®. Roxane therefore submits the following comments.

There is no legal or scientific basis for the Agency to impose any of the requirements that Jazz has requested. FDA already has rejected Jazz's assertion that it cannot accept an ANDA for review unless and until it publishes bioequivalence requirements in the Orange Book, and Jazz's petition provides no basis for revisiting that issue. Our comments with respect to that issue therefore highlight two different points: first, that the D.C. Circuit rejected claims that the statute's Orange Book publication provisions are dispositive, and second, that Jazz lacks standing to raise this issue.

Jazz's claims that FDA should impose *in vivo* bioequivalence testing requirements for ANDAs referencing Xyrem® are also without merit. The petition offers no credible scientific basis for concluding that modest variations "in manufacturing process, pH, excipients, impurities, degradants, or contaminants" would have any clinically meaningful impact on the product's absorption characteristics. This is especially true because Xyrem®'s dose-preparation instructions require patients to dilute each sample of the product by some 667-to-1333 percent on a volume-by-volume basis with ordinary tap water, which is uncontrolled and highly variable in quality.

The Agency should recognize Jazz's petition for what it is: a transparent effort to delay generic competition that on its face fails to raise any colorable scientific or regulatory issues. The petition should be denied.

ARGUMENT

A. FDA's Failure To Publish Bioequivalence Requirements In The Orange Book Has No Impact On FDA's Ability To Accept For Review, Review, Or Approve An ANDA Referencing A Previously Approved Drug Product.

FDA already has rejected Jazz's claim that the Agency cannot accept for review, review, or approve an ANDA referencing a listed drug product unless and until FDA also publishes in the Orange Book a statement indicating whether it intends to require *in vitro* and/or *in vivo* bioequivalence studies as a condition of approval for ANDAs referencing that listed drug product. *See* Letter from J. Woodcock to T. Doyle, Docket No. FDA-2006-P-0007, at 60-61 (Apr. 9, 2012) [the "Vancomycin Letter Decision"]. This has been FDA's position since Hatch-Waxman first was enacted in 1984, and neither Congress nor the courts have taken any steps to set aside the Agency's implementation of this aspect of the Hatch-Waxman scheme. Nor is there any serious question that FDA is correct: The statute conditions submission of an ANDA only on the existence of a previously approved "*drug* listed under paragraph (7)," 21 U.S.C. § 355(j)(2)(A)(i) (emphasis added)--not on whether the list *also* contains *general bioequivalence standards for ANDAs* that will reference that drug--and there is in any event no plausible basis for thinking that Congress would have intended to delay the potential onset of generic competition where FDA fails within days of approving an NDA to publish an initial bioequivalence approach for ANDAs that by law may not be submitted for years. *See, e.g.*, 21 U.S.C. § 355(F) (data exclusivity periods); *see also Andrx Pharm., Inc. v. Biovail Corp. Int'l*, 256 F.3d 799, 809 (D.C. Cir. 2001) ("'Congress sought to get generic drugs into the hands of patients at reasonable prices--fast.'") (quoting *In re Barr Labs.*, Inc., 930 F.2d 72, 76 (D.C. Cir. 1991)).

In addition to the other grounds FDA already has advanced in rejecting this contention, two other points bear note. First, the D.C. Circuit has rejected similar claims concerning the FDCA's Orange Book publication provisions. In *Teva Pharmaceuticals, USA, Inc. v. Leavitt*, 548 F.3d 103 (D.C. Cir. 2008), an ANDA applicant claiming entitlement to 180-day marketing exclusivity asserted that it was entitled to maintain a Paragraph IV certification to a patent that the brand manufacturer had asked FDA to delist from the Orange Book because that patent remained physically listed in the Orange Book at the time it submitted its Paragraph IV certification. Like Jazz, whose petition contends that the Orange Book's listings dictate which NDA products are subject to the submission of an ANDA, the generic manufacturer in *Leavitt* asserted that the Orange Book's patent listings control which patents are subject to the submission of a Paragraph IV certification. In the applicant's words:

> [T]he statute's patent-publication requirements [21 U.S.C. §§ 355(j)(7)(A)(i)-(iii)] are an integral component of the statutory regime, designed specifically to put potential generic applicants on notice of the patent barriers that might block market entry--and for which patent-challenging Paragraph IV certifications are required if the applicant wishes to launch a generic product before patent expiry and with 180-day exclusivity. That, of course, explains why FDA's own Hatch-Waxman regulations ... expressly require generic applicants to submit "an

> appropriate certification *for each listed patent*," even if the applicant disagrees about "the correctness of the patent information ... *published by FDA in the list*."

Br. of Appellees, *Leavitt*, 2008 WL 2828515, *4 (filed July 21, 2008) (quoting 21 C.F.R. § 314.53(f) (with emphasis in original)).

Despite the seemingly clear regulatory link between the patent-listing and patent-certification requirements, however, the D.C. Circuit held that "[i]nadvertent failure by the agency to meet its separate publication requirement cannot defeat facts [*i.e.*, the lack of a patent that claimed the listed drug as of the time the Paragraph IV certification was submitted]." *Leavitt*, 548 F.3d at 107. And it went on to explain that "the Agency's failure to list a patent after the NDA holder provided the information would not deprive the branded drug manufacturer of its rights under paragraph IV." *Id.* at 108. As the court thus held, the status of a patent as being "listed" or "not listed," and the substantive consequences that follow, turn not on whether FDA actually has published that patent in the Orange Book, but on the underlying "reality" that "reflect[s] the Agency's most current information." *Id.* at 105. There is thus no basis for "punishing the Agency's inadvertence" in such circumstances--least of all where doing so "would otherwise preclude price competition." *Id.* Suffice it to say, there is no basis for treating the bioequivalence publication requirement any different than the patent publication requirement (both, after all, are critical to the contents of an ANDA referencing a previously approved drug product), and it would be arbitrary and capricious to adopt a rule in this context that both FDA and the courts have rejected in that context.

Even if there were grounds for contesting FDA's longstanding interpretation of the bioequivalence publication requirement, Jazz has no standing to raise those issues. For purposes of assessing standing under the APA, it is well-established that a court presented with a challenge to agency action must determine "whether the interest sought to be protected by the complainant is arguably within the zone of interests to be protected or regulated by the statute or constitutional guarantee in question." *Ass'n of Data Processing Serv. Orgs. v. Camp [ADAPSO]*, 397 U.S. 150, 153 (1970). In turn, "[t]he relevant zone of interests is determined 'not by reference to the overall purpose of the Act in question ... but by reference to the particular provision' at issue." *Ass'n of Am. Physicians & Surgeons, Inc. v. FDA*, 539 F. Supp. 2d 4, 18 (D.D.C. 2008) (quoting *Grand Council of Crees (of Quebec) v. FERC*, 198 F.3d 950, 956 (D.C. Cir. 2000) (itself quoting *Bennett v. Spear*, 520 U.S. 154, 175-76 (1997))), *aff'd* 358 Fed. Appx. 179 (D.C. Cir. 2009).

There is no question that Jazz falls outside the zone of interests protected by the statute's bioequivalence publication provision. As Jazz instead concedes explicitly in its petition, the purpose of the publication requirements is "to ensure *ANDA applicants* (and the general public) know about bioequivalence requirements" in order to facilitate and expedite *their* submission of generic applications referencing previously approved drugs. Pet. at 13 (emphasis added; citing H.R. REP. No. 98-857, pt. 2, at 17 (1984)). And as Jazz elsewhere observes, "multiple preamble statements reflect FDA's own recognition that publication of bioequivalence requirements was intended *to guide prospective ANDA applicants*." *Id.* at 13 n.92 (additional citations omitted).

In other words, the provision requiring FDA to disclose bioequivalence requirements is designed *to help* ANDA applicants by alerting them to the Agency's preferred method for demonstrating bioequivalence--not to erect a barrier that arbitrarily forestalls the approval of competing products. Where an applicant opts to submit an ANDA prior to the publication of bioequivalence standards, it thus assumes a risk that FDA ultimately might adopt bioequivalence requirements that the applicant did not anticipate at the time it filed. But that is the applicant's choice--and *its* interest to defend in the event it wishes to obtain greater certainty before filing an ANDA--not one that in any sense is designed to protect the interest of a brand manufacturer who wishes to thwart the approval of a competing product. Accordingly, Jazz has no standing to challenge FDA's longstanding interpretation of this aspect of the statute, and its otherwise meritless arguments can and should be rejected.

B. There Is No Colorable Scientific Basis For Requiring Applicants To Conduct *In Vivo* Bioequivalence Studies For Sodium Oxybate ANDAs That Differ From Xyrem® In Manufacturing Process, pH, Excipients, Impurities, Degradants Or Contaminants.

Jazz's petition does not provide any credible scientific basis for requiring applicants to conduct *in vivo* bioequivalence studies for sodium oxybate oral solution ANDAs that reference Xyrem®, and FDA therefore should deny the petition's request to require such studies as a condition of approval. As the Agency long has recognized, "[f]or certain drug products, the *in vivo* bioavailability or bioequivalence of the drug product may be self-evident." 21 C.F.R. § 320.22(b). In those circumstances, FDA's regulations expressly mandate that "FDA *shall* waive the requirement for the submission of evidence obtained *in vivo* measuring the bioavailability or demonstrating the bioequivalence of these drug products." *Id.* (emphasis added). Three criteria control the inquiry here:

> 1. Is the proposed ANDA product "a solution for application to the skin, *an oral solution*, elixir, syrup, tincture, a solution for aerosolization or nebulization, a nasal solution, or similar other solubilized form," *id.* § 320.22(b)(3)(i) (emphasis added);
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> 2. Does the proposed ANDA product "[c]ontain[] an active drug ingredient *in the same concentration and dosage form* as a drug product that is the subject of an approved [NDA]," *id.* § 320.22(b)(3)(ii) (emphasis added); and
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> 3. Does the proposed ANDA product "[c]ontain[] no inactive ingredient or other change in formulation from the drug product that is the subject of the approved [NDA] that may *significantly affect* absorption of the active drug ingredient or active moiety for products that are systemically absorbed," *id.* § 320.22(b)(3)(iii) (emphasis added)?

Jazz does not dispute that Roxane's sodium oxybate ANDA readily satisfies the first two criteria--and for good reason. Roxane's ANDA is of course for an oral solution, and Roxane's formulation contains sodium oxybate in the same concentration and dosage form as Xyrem®. The only issue raised by Jazz's challenge to the grant of a waiver is thus whether there are any

differences between the Xyrem® formulation and that of Roxane's proposed ANDA product "that may *significantly affect* absorption of the active drug ingredient" in this systemically absorbed product. *Id.* (emphasis added).

In our view, it is self-evident that Jazz's speculative claims regarding the impact on *in vivo* absorption of any differences in the manufacturing process, pH, excipients, impurities, degradants, or even contaminants are without merit given the proper, FDA-approved dosage administration for this product. As a threshold matter, it is strange even to question whether an oral solution containing *only* sodium oxybate, malic acid, and water is so exquisitely sensitive that trace differences in such factors would require multiple *in vivo* bioequivalence studies in humans under both fasted and fed study conditions merely *to confirm* the lack of impact on bioavailability. But it is astonishing for Jazz to suggest that the product is indeed so exquisitively sensitive to these variables that such tests are required, given that the product's instructions for preparation and dose administration require patients to dilute the product by some 667-to-1333 percent on a volume-by-volume basis with ordinary tap water--which of course is uncontrolled and highly variable in quality.

In short, any nuances that the product's formulation may have by virtue of its manufacturing process, pH, excipient, degradants, or contaminants are completely and utterly overwhelmed by the preparation of the dosage by the patient before consuming the product. And whether the impact of formulation/product differences relate to the differing amounts of GBL and clinical onset, the absorption of GHB via drug transporters, any possible impact on the food effect, or even the variability that could arise if multiple generic products were approved, any and all of those issues are clinically insignificant given the approved dosage range of Xyrem® and the wide variability that the product is subjected to when an unspecified source of water is used to dilute the concentrated product.

1. The Fact That Xyrem® Must Be Diluted With Tap Water Before Administration Decisively Undermines Any Claim That The Product Is So Sensitive That *In Vivo* Testing Is Necessary To Establish The Lack Of A Significant Impact On Product Absorption.

According to its product label, Xyrem® "contains 500 mg of sodium oxybate per milliliter of USP Purified Water, neutralized to pH 7.5 with malic acid" to form an aqueous solution.[1] Even if referred to as consisting of "a monocarboxylic acid, dicarboxylic acid, and a sodium counterion," Pet. at 16, Xyrem® is not sophisticated in the pharmaceutical sense. It is not a suspension with various wetting agents, preservatives, viscosity agents, taste-masking components, etc. It is simply a clear solution with two ingredients, one of which is the active ingredient dissolved in water and the other an acidulant used to adjust the pH.

Jazz nonetheless asserts that formulation differences between Xyrem® and a proposed generic sodium oxybate product, even at the trace level of contaminants and degradants, may have a significant affect on the product's *in vivo* absorption--that is, that the product is so

[1] *See, e.g.*, Xyrem® Full Prescribing Information (the "Xyrem® PI"), at 2, *available at* http://www.xyrem.com/images/XYREM%20PI_2011.pdf (last visited Oct. 24, 2012).

extremely sensitive that it would be inappropriate to grant a waiver. Pet. at 17-22. But there is no evidence to support that proposition, and quite compelling evidence that refutes Jazz's suggestion that its *in vivo* absorption might be affected by the type of common differences between generic and branded products that result, for example, from different manufacturing processes.

In particular, and unlike many solution-based products (including the many far more complex solution-based products that FDA has approved without requiring *in vivo* bioequivalence studies), Xyrem® is not formulated or intended to be administered intact. Instead, the Dosage and Administration section of the product's FDA-approved prescribing information provides that the product must be diluted with a significant quantity of water before it is consumed by patients. More specifically, the package insert recommends a starting dose of "4.5 g/night divided into two equal doses of 2.25 g [which] can then be increased to a maximum of 9 g/night in increments of 1.5 g/night (0.75 g per dose)," and it instructs patients to divide and prepare the doses as follows:

> Prepare both doses of Xyrem prior to bedtime. Each dose of Xyrem ***must be diluted with two ounces (60 mL, 1/4 cup, or 4 tablespoons) of water*** in the child-resistant dosing cups provided prior to ingestion. The first dose is to be taken at bedtime and the second taken 2.5 to 4 hours later; both doses should be taken while seated in bed. Patients will probably need to set an alarm to awaken for the second dose. ***The second dose must be prepared prior to ingesting the first dose, and should be placed in close proximity to the patient's bed.*** After ingesting each dose patients should then lie down and remain in bed.

Xyrem® PI at 8 (emphasis added). On a volume-by-volume basis, these instructions for the creation of the final dosage thus provide for dilution with ordinary tap water by 667 percent (for each half of the 9 g/night dosage) and 1333 percent (for each half of the 4.5 g/night dosage).[2] In addition, the instructions provide no guidance with respect to water temperature, and by requiring that both doses be prepared at the same time, virtually ensure that the two doses will be consumed at different temperatures (the latter dose will reach room temperature by the time it is consumed).

The obvious problem with Jazz's position is that there is tremendous variability in the quality and characteristics of tap water from city to city and state to state. The quality of water drawn from residential wells can be even more variable. Given Jazz's purported concern about even modest differences in pH, it bears particular note that pH levels in public water systems vary dramatically; the EPA does not regulate the pH in drinking water, but recommends that public water systems maintain pH levels ranging from 6.5 to 8.5.[3] In addition to pH, water quality testing assays metals such as barium, calcium, iron and magnesium which are from

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[2] For the 9 g/night dosage, 9 mL of product at a concentration of 0.5 g/mL is required to obtain a single 4.5 g dose. Each 9.0 mL aliquot then is diluted with 60mL of water. A sample volume of 4.5mL is used for each of the two dosage preparations for the 4.5g/night regimen.

[3] *See, e.g.*, U.S. Environmental Protection Agency, *Secondary Drinking Water Regulations: Guidance for Nuisance Chemicals*, *available at* http://water.epa.gov/drink/contaminants/secondarystandards.cfm (last visited Oct. 24, 2012).

erosion of natural deposits, and levels vary greatly. Chloride from road salt and chlorine organic chemicals attributed to drinking water chlorination (bromochloroacetic acid, chloral hydrate, haloacetonitriles, halogenated ketones) also are assessed and likewise can vary widely.[4]

Without belaboring the point, the fact that Xyrem® is designed to be substantially diluted with ordinary, uncontrolled tap water prior to dosing forecloses any conceivable claim that the product is so exquisitely sensitive to pH, excipients, impurities, degradants or containments that it would be inappropriate to approve a generic version of the product without *in vivo* bioequivalence studies under both fed and fasting study conditions.

2. None Of The Particular Formulation Characteristics Jazz Highlights Are Likely To Significantly Affect *In Vivo* Absorption.

a. Levels of GBL

It has been confirmed *in vitro* that GHB and GBL exist in equilibrium. Jazz notes that GHB degrades to gamma-butyrolactone (GBL), Pet. at 17 n.106 (through a pH-dependent equilibrium interconversion[5]), and *in vivo* GBL is directly metabolized to GHB. *Id.* at 17.[6] In strongly acidic conditions (such as in the stomach), the equilibrium readily shifts converting GHB into GBL.[7] Jazz argues that because GBL is more lipophilic than GHB, it is more rapidly absorbed and that products which differ in the amount of GBL could result in a more rapid and higher plasma levels of GHB, thereby accelerating the onset of action. *Id.* Jazz implies that even a small difference in GBL that might occur between multisource sodium oxybate products could result in more rapid onset of drug action and safety concerns. For this reason, Jazz states the GBL plasma levels between products needs to be characterized with respect to impact on sleep onset. *Id.*

As set forth above, however, this claim cannot be squared with the fact that Xyrem® must be substantially diluted with pH-variable tap water prior to administration, which in turn influences pH-dependent interconversion to GBL. Accordingly, any subtle variability in pH between Xyrem® and generic sodium oxybate products that may exist *ab initio* will be overwhelmed once the product is prepared for dosage and administration, and almost certainly is clinically insignificant.

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[4] *See, e.g.*, New York City Department of Environmental Protection, *New York City 2011 Drinking Water Supply and Quality Report*, at 10, *available at* www.nyc.gov/html/dep/pdf/wsstate11.pdf (last visited Oct. 24, 2012) (reporting ranges for several dozen chemicals/contaminants, and among other things indicating a pH range of 6.7-9.8).

[5] *See* Ciolina LA, Mesmer MZ, Satzger RD, Machal AC, McCauley HA, Mohrhaus AS, The chemical interconversion of GHB and GBL; forensic issues and implications. *J Forensic Sci. 2001; 46(6): 1320.*

[6] Ciolina studied the reaction *in vitro* and concluded that "GBL hydrolysis occurs under acidic, basic, and neutral [*in vitro*] conditions with a rate and extent of conversion to GHB varying widely according to the solution pH." *See* Ciolina at 1322.

[7] Ciolina at 1319.

Jazz conducted a study examining the effect of the proton pump inhibitor omeprazole on the pharmacokinetics of sodium oxybate.[8] That study found that omeprazole does not significantly impact the bioavailability of sodium oxybate or the frequency and severity of adverse effects, and concluded that the dosage of sodium oxybate does not require adjustment when given concomitantly with drugs that reduce gastric acidity. This suggests that while the there may indeed be a relationship between product pH and degradants like GBL, any clinical effect is unlikely within labeled dosing parameters if there wasn't a significant impact observed with a reduction in gastric acidity.

Additional support for the lack of clinical sensitivity can be found in comments to FDA in an Advisory Committee Briefing Document in July 2010:

> "In the narcolepsy clinical development program, the respiratory depressant effects of sodium oxybate, when administered at recommended doses, were assessed in 21 patients with narcolepsy, and no dose-related changes in oxygen saturation were demonstrated in the group as a whole. In the randomized controlled Trials 3 and 4 (OMC-SXB-15 and OMC-SXB-22, respectively), a total of 40 narcolepsy patients were included with a baseline apnea/hypopnea index of 16 to 67 events per hour indicative of mild to severe sleep-disordered breathing. None of the 40 patients had a worsening of their respiratory function as measured by apnea/hypopnea index and pulse oximetry while receiving sodium oxybate at dosages of 4.5 to 9 g/night in divided doses[9].

This demonstrates that even if the dosage (and presumably the degradants and contaminants including GBL) was doubled from 4.5g to 9.0 g/night in divided doses there was not a dose-related change in oxygen saturation or a worsening of respiratory function.

In their Citizen Petition, Jazz does not attempt to quantify potential differences in absorption that may be of clinical concern. Jazz failed to see a clinical impact on the bioavailability of sodium oxybate while given concomitantly with a proton pump inhibitor which affects gastric acidity and therefore the conversions of sodium oxybate to GBL. Jazz also failed to identify dose related changes in oxygen saturation or any other clinically recognizable adverse event over a 2-fold range of clinically indicated dosages (4.5 to 9 g/night in divided doses). Therefore the concern that small differences in GBL might result in a more rapid onset of drug action or other safety concerns seems unfounded.

b. Active Transport of GHB

Jazz also spends several pages of its petition explaining the role of drug transporters in influencing drug absorption, distribution, metabolism and elimination. Jazz then cites a paper by

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[8] Borgen LA, Morrison D, Lai A. The Effect Of Omeprazole On The Bioavailability Of Sodium Oxybate. Clin Pharm & Ther 2004;75(2).

[9] Jazz Pharmaceuticals - NDA 22-531. Sodium Oxybate Oral Solution. Joint Meeting of the Arthritis Drugs Advisory Committee And the Drug Safety and Risk Management Advisory Committee. 20 August 2010.

Morris[10] as indicating drug transporters are critical to the absorption of GHB, and asserts that "consequently, generic sodium oxybate formulations that differ from Xyrem in their manufacturing process, pH, excipients, impurities, degradants and contaminates may result in different therapeutic concentrations, i.e. bio*in*equivalence." Pet. at 18. But Jazz provides no explanation as to *how* any of those factors might significantly affect the interaction between transporters and the product's pharmacologically active components, and indeed fails even to identify *which* of those characteristics might significantly impact the interaction between transporters and the product's active ingredient. Given Jazz's inability to identify any difference that might significantly impact transporter-based drug or excipient interactions, there is thus no basis for requiring FDA to require an evaluation of "any differences in formulation between a generic sodium oxybate product and Xyrem with the potential to result in transporter-based drug or excipient interactions." *Id.* at 20.

Indeed, it is not even clear that the Morris paper provides substantial support for Jazz's claims. That paper principally addresses the MCT1 transporter as the principle isoform involved in GHB renal reabsorption and postulates how MCT substrates of l-lactate may provide a novel strategy in detoxification. In a single paragraph, Morris briefly cites published and unpublished data in Caco-2 cells *suggesting* that GHB's absorption is mediated *in part* by MCTs in the human intestine. We do not disagree that it is important to understand the role of transporters, and also that the Lam[11] paper suggest that GHB is transported by MCTs in Caco-2 cells and we support FDA's work in this area. We do not agree that these findings *a priori* demonstrate Jazz's assertion and do not remotely justify a refusal to grant a standard waiver with respect to this product--especially not in light of the fact that Xyrem® must be diluted with a significant quantity of uncontrolled tap water prior to patient administration, which introduces substantial pH variability and introduces an unknown array of varying contaminates that overshadow any relative minor difference that may occur across ANDA-approved sodium oxybate products at the transporter level.

c. Food Effect

Jazz next contends that food has a significant effect on the bioavailability of GHB, Pet. at 20-21, and cites a paper by Custodio[12] indicating that high-fat meals can decrease intestinal uptake of drugs like GHB by inhibiting anionic transporters like MCTs. *Id.* at 21. Jazz therefore speculates that these food effects might differ for generic sodium oxybate solutions that differ in excipients and pH. *Id.* But Jazz again provides no basis for its suggestion that minor variations in excipients or pH are likely to have any significant impact--indeed, it acknowledges that there has been no proof of this effect, *see id.* ("[C]hanges in absorption continue to be difficult to model and are an area of active research")--much less that these variations can be anticipated to

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

[11] Lam WK, Felmlee MA, Morris ME. Monocarboxylate transporter-mediated transport of gamma-hydroxybutyric acid in human intestinal Caco-2 cells. Drug Metab and Dispos. 2012 Mar;38(3):441-7.

[12] Custodio JM, WU CY. Benet LZ. Predicting drug disposition, absorption/elimination/transporter interplay and role of food on drug absorption. Adv Drug Deliv Rev. 2008 March 17; 60(6): 717-33.

have any clinically significant effect given that Xyrem®'s instructions for dosage and administration require the product to be significantly diluted with uncontrolled tap water, and given that subsequent changes in stomach and gastrointestinal pH following meals of widely varying caloric and fat quantity will far overwhelm possible pH differences between Xyrem® and generic sodium oxybate solution products.

d. REMS Issues

As if to acknowledge that its "scientific" arguments are based on unsupported speculation, Jazz next asserts that FDA should apply an unusually stringent approach to its *in vivo* bioequivalence waiver determination simply because Xyrem® is subject to a REMS program requirement that includes elements to assure safe use ("ETASU"). Pet. at 21-22. But the standards for granting a waiver do not depend on whether a given product is subject to a REMS containing ETASU, and as Jazz well knows, the Agency imposed ETASU for this product because Xyrem® and other sodium oxybate products are subject to a risk of drug abuse and possible diversion that carry risks of serious adverse events--not because the product itself is especially dangerous or otherwise extraordinarily sensitive. *See, e.g.*, Xyrem® PI at 2 ("!WARNING: Central nervous system depressant with abuse potential. Should not be used with alcohol or other CNS depressants. Sodium oxybate is GHB, a known drug of abuse. Abuse has been associated with some important central nervous system (CNS) adverse events (including death).") (emphasis in original). Needless to say, those concerns have no bearing on the waiver determination, and we respectfully submit that the Agency should reject Jazz's attempt to mask the fact that drugs in solution form pose a minimal risk for potential bioavailability differences by invoking the product's abuse-potential-based ETASU requirements.

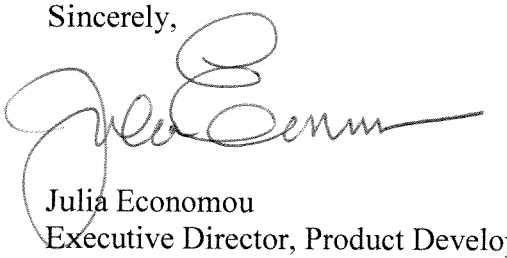
e. Multiple Generics

Finally, Jazz expresses concern that "FDA might approve multiple [generic sodium oxybate] products with various different formulations" unless it promulgates stringent *in vivo* bioequivalence testing requirements, and that doing so would require FDA "to assess each individual formulation difference in each generic drug product." *Id.* at 22. That assertion is utterly without merit, and provides no basis for the requested actions. After all, the same thing could be said any time FDA grants a waiver under 21 C.F.R. § 320.22(b), and taken seriously, would prevent FDA from ever granting such a waiver. At the end of the day, the fact remains that each ANDA product referencing Xyrem® will remain subject to a rigorous CMC assessment by the Agency, just like every oral drug product that is not exempted from the *in vivo* bioequivalence study requirement--ensuring the safety and efficacy of these products consistent with the well-established regulatory criteria for granting such a waiver.

CONCLUSION

The petition should be denied for the foregoing reasons.

Sincerely,



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