



DEPARTMENT OF HEALTH & HUMAN SERVICES

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Food and Drug Administration
10903 New Hampshire Avenue
Building #51
Silver Spring, MD 20993

Philip J. Honerkamp
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Re: Docket No. FDA-2012-P-0499

Dear Mr. Honerkamp:

This letter responds to your citizen petition (petition) received May 18, 2012,¹ in which you request that the Food and Drug Administration (FDA or Agency): (1) immediately publish in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book") bioequivalence requirements specifying whether in vitro or in vivo bioequivalence studies, or both such studies, are required for abbreviated new drug applications (ANDAs) referencing XYREM (sodium oxybate) oral solution; (2) not accept for review, review, or approve any ANDA referencing XYREM (sodium oxybate) oral solution until FDA publishes such bioequivalence requirements in the Orange Book; and (3) require both fed and fasted in vivo bioequivalence studies, and a demonstration of onset of drug action equivalent to XYREM (sodium oxybate) oral solution, for any sodium oxybate drug product for which approval is sought in an ANDA if such drug product differs from XYREM in manufacturing process, pH, excipients, impurities, degradants or contaminants.²

FDA has considered the information provided in your petition, comments to the petition docket submitted by Roxane Laboratories,³ the relevant statute and regulations, and other information available to the Agency, and, for the reasons set forth below, denies your petition.

I. BACKGROUND

A. XYREM

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,

¹ Citizen Petition submitted by P. J. Honerkamp on behalf of Jazz Pharmaceuticals, Docket No. 2012-P-0499 (May 18, 2012). The Agency also received a second citizen petition involving XYREM submitted on behalf of Jazz Pharmaceuticals on July 10, 2012, and will address the issues raised therein in a separate response.

² Petition, at 1-2.

³ Comments of Roxane Laboratories to Docket No. 2012-P-0499 (Oct. 24, 2012).

2005, the Agency 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.⁴ Recreational abuse of GHB has been associated with adverse CNS events, including life-threatening respiratory depression, coma, and death.⁵

GHB is the pharmacologically active metabolite of both gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD), both of which have also been abused recreationally.⁶ GHB and GBL are interconverted in aqueous solution via hydrolysis and intramolecular esterification reactions.⁷

XYREM is a schedule III controlled substance⁸ due to its currently accepted medical use, but even at recommended doses, it has been associated with confusion, depression, and other neuropsychiatric events.⁹

B. Statutory and Regulatory Basis for Approving ANDAs

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. To obtain approval, an ANDA applicant is not required to submit evidence to establish the safety and effectiveness of the drug product, as is required for an NDA. Instead, an ANDA relies on FDA's previous finding that the reference listed drug (RLD) is safe and effective. To rely on this finding, the ANDA must contain (with certain exceptions not relevant here) information to show that the proposed drug has the same active ingredient(s), indications, route of administration, dosage form, strength, and labeling as

⁴ 21 USC § 812(b)(1).

⁵ 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 Manif.* 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.

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

⁷ Ciolino, LA; Mesmer, MZ; Satzger, RD; Machal, AC; McCauley, HA; Mohrhaus, AS. The chemical interconversion of GHB and GBL: forensic issues and implications. *J Forensic Sci.* 2001; 46(6):1315-1323.

⁸ 21 USC § 812(b)(3).

⁹ XYREM Package Insert, at 1, 10, available at

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

the RLD (sections 505(j)(2)(A) and (j)(4) of the FD&C Act), and is bioequivalent (section 505(j)(2)(A)(iv) of the FD&C Act) to the RLD. The basic assumption underlying the Hatch-Waxman Amendments is that bioequivalent drug products that meet these criteria are therapeutically equivalent and may be substituted for each other.

Under the FD&C Act, a generic¹⁰ drug product is bioequivalent to the RLD “if the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient” (section 505(j)(8)(B)(i) of the FD&C Act). FDA regulations at 21 CFR 320.1(e) specify that two drug products are bioequivalent if there is an

absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.¹¹

The bioequivalence requirement for an ANDA and procedures for determining bioequivalence are set forth in 21 CFR 314.94(a)(7) and 21 CFR part 320, respectively. Subsection 320.24(a) provides that FDA may require in vivo testing, in vitro testing, or both, to establish bioequivalence, and requires that an applicant use the most accurate, sensitive and reproducible method available.¹² Subsection 21 CFR 320.24(b) sets out various methods of establishing bioequivalence in generally descending order of accuracy, sensitivity, and reproducibility including pharmacokinetic studies, pharmacodynamic studies, comparative clinical trials, and in vitro studies. In addition, subsection 320.24(b)(6) states that FDA has the discretion to use “[a]ny other approach deemed adequate by FDA to . . . establish bioequivalence.” The courts have expressly upheld FDA’s discretion to determine the appropriate bioequivalence methodology for products (see, e.g., *Schering Corp. v. FDA*, 51 F.3d 390, 397-400 (3d Cir. 1995)).¹³

If FDA determines that in vivo data is the appropriate means of demonstrating bioequivalence for a product or product class, 21 CFR 320.21(f) provides that applicants may apply for a waiver of such in vivo requirement consistent with 21 CFR 320.22,¹⁴ which in turn directs that FDA “must” waive any in vivo requirement upon a subsequent showing that the individual applicant’s product meets certain additional criteria.¹⁵ For

¹⁰ The term *generic* is used in this petition response to refer to drug products for which approval is sought in an ANDA submitted under section 505(j) of the FD&C Act.

¹¹ See also 21 CFR 320.23(b).

¹² 21 CFR 320.24(a).

¹³ See also *Fisons Corp v. Shalala*, 860 F. Supp. 859, 866-67 (D.D.C. 1994) (“[T]he factual determination of how bioequivalence is determined properly rests within the FDA’s discretion.”); *Astellas Pharma US, Inc. v. FDA*, 642 F. Supp. 2d 10, 19 (the “high degree of deference” given to FDA’s scientific determinations “has been applied to the FDA’s determinations regarding which methodologies it determines are needed to test the bioequivalency of a given generic”).

¹⁴ 21 CFR 320.21(f) (“[i]nformation to permit FDA to waive the submission of evidence measuring the in vivo bioavailability or demonstrating the in vivo bioequivalence shall meet the criteria set forth in 320.22”).

¹⁵ 21 CFR 320.22(a).

example, if FDA requires in vivo data for an oral solution, FDA generally must waive that requirement if the ANDA applicant demonstrates that its individual product contains the same active ingredient in the same concentration and dosage form as the RLD, and, for systemically absorbed products, contains no inactive ingredient or other change in formulation from that of the RLD that may significantly affect absorption of the active ingredient or moiety.¹⁶ Even in instances in which such additional criteria are met, however, FDA retains final discretion to require in vivo data if the Agency determines that any differences between the drug product and the RLD may affect the bioequivalence of the drug product.¹⁷ Subsection 320.22(e) provides that FDA “may” waive any Agency-imposed in vivo bioequivalence data requirement for a particular product “for good cause ... if waiver is compatible with the protection of the public health.”¹⁸

The Agency’s authority to make bioequivalence determinations on a case-by-case basis using in vivo, in vitro, or both types of data enables FDA to effectuate several long-recognized policies that protect the public health: (1) refraining from unnecessary human research when other methods of demonstrating bioequivalence meet the statutory and regulatory standards;¹⁹ (2) permitting the Agency to use the latest scientific advances in approving drug products;²⁰ (3) protecting the public by ensuring only safe and effective generic drugs are approved for marketing;²¹ and (4) making more safe and effective generic drugs available.²²

¹⁶ 21 CFR 320.22(b)(3). See generally, 21 CFR 320.22(b)-(d) (additional categories of products for which waivers of an in vivo data requirement may be sought).

¹⁷ 21 CFR 320.22(f).

¹⁸ 21 CFR 320.22(e). FDA also has the general discretion to waive any requirement set forth in subpart C of part 314, which sets forth the approval scheme for ANDAs. See 21 CFR 314.99(b)) (“[a]n applicant may ask FDA to waive under this section any requirement that applies to the applicant under 314.92 through 314.99. The applicant shall comply with the requirements for a waiver under 314.90”). As FDA noted with respect to the analogous 21 CFR 314.90, such waivers are intended “to give applicants the flexibility to seek alternative ways of complying with the regulatory requirements for drug approval.” *New Drug and Antibiotic Regulations; Final Rule*, 50 FR 7452, 7490 (Feb. 22, 1985).

¹⁹ 21 CFR 320.25(a) (“guiding principle” that “no unnecessary human research should be done” expressed in regulation addressing conduct of an in vivo bioavailability study); *Abbreviated New Drug Application Regulations; Proposed Rule*, 54 FR 28872, 28883 (July 10, 1989) (ANDA Proposed Rule) (in discussing section 320.22, states “the agency does not believe that Congress intended that unnecessary human research be conducted ... if the agency concludes that bioequivalence can be demonstrated by in vitro tests”).

²⁰ *Bioavailability and Bioequivalence Requirements: Procedures for Establishing a Bioequivalence Requirement; Final Rule*, 42 FR 1624, 162 (Jan. 7, 1977) (in promulgating final bioequivalence regulations, FDA noted that “[a]s with all new regulations relating to an evolving science, the Commissioner reserves the right to consider other factors that may indicate the need to establish a bioequivalence requirement”).

²¹ *Schering Corp. v. Sullivan*, 782 F. Supp. 645, 650 (D.D.C. 1992), (citing as one underlying policy of the Hatch-Waxman Amendments, to “ensure the safety of these drugs before they are substituted for their name-brand counterparts”).

²² *Id.* (purposes of Hatch-Waxman Amendments are “to make more inexpensive generic drugs available” and “to ensure the safety of these drugs”); *Fisons Corp. v. Shalala*, 860 F. Supp. at 866-67 (D.D.C. 1994) (bioequivalence waiver provision “comports with the structure and broader policy objectives of the Hatch-Waxman Act” including making safe and affordable generic drugs available).

C. FDA Guidance on Food-Effect Studies

FDA's guidance for industry *Food-Effect Bioavailability and Fed Bioequivalence Studies* (Dec. 2002) (Food-Effect Guidance)²³: (1) provides general information and recommendations on how to meet the bioavailability and bioequivalence requirements in the regulations as they apply to oral dosage forms, (2) discusses when food-effect bioavailability and fed bioequivalence studies should be conducted, and (3) details how the studies should be designed and the resulting data analyzed.

Food can change the bioavailability of a drug and influence bioequivalence among drug products.²⁴ The nutrient and caloric content of the meal, the meal volume, and the meal temperature can cause physiological changes in the gastrointestinal tract that affect drug product transit time, luminal dissolution, drug permeability, and systemic availability. The food effect is usually greatest when the drug product is administered immediately following a high-fat, high-calorie meal. Accordingly, when in vivo data is required, FDA generally expects that unless certain exceptions apply, ANDA applicants also will conduct a bioequivalence study under fed conditions for orally administered drug products in addition to a bioequivalence study under fasting conditions. The exceptions described in the Food-Effect Guidance include the following:

- When both test product and RLD are rapidly dissolving, have similar dissolution profiles, and contain a drug substance with high solubility and high permeability (i.e., Biopharmaceutics Classification System (BCS) Class 1)
- When the DOSAGE AND ADMINISTRATION section of the RLD labeling states that the product should be taken only on an empty stomach, or
- When the RLD labeling does not make any statements about the effect of food on absorption or administration.²⁵

For recently-approved RLDs, these exceptions reflect situations in which FDA has identified that the drug is unlikely to have a food effect (e.g., BCS Class 1 drugs or drugs without a statement of food effect on the label), or in which the drug will not be taken with food when used as indicated (e.g., when the labeling directs that the drug should be taken on an empty stomach). In such instances, fasted studies alone may be sufficient to ensure bioequivalence when the proposed generic drug is used under conditions prescribed in the RLD's labeling. But for older drugs, the absence of food-related statements in the labeling may be due to the fact that in the past conducting food-effect

²³ Available on the Internet at

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

²⁴ See BA/BE Guidance, at 17. Usually, a single-dose, two-period, two-treatment, two-sequence crossover study is recommended for food-effect bioavailability and bioequivalence studies. Id..

²⁵ Food-Effect Guidance, at 3-4.

studies was a relatively rare practice. The Agency may therefore recommend that ANDA applicants referencing such older drugs conduct both fed and fasted bioequivalence studies even where the RLD's labeling does not make any food-effect statements.

D. Therapeutic Equivalence Evaluations

Subsection 505(j)(7)(A)(i) of the FD&C Act requires the Agency to publish the bases for its evaluation of the bioequivalence of generic products. As indicated in subsection 320.24(a) of FDA's bioequivalence regulations, FDA fulfills this requirement in the Orange Book in the form of code letters, referred to as therapeutic equivalence (TE) codes.²⁶ FDA publishes this information at the time a generic product referencing an RLD is approved.

Specifically, each approved generic drug is assigned a TE code that reflects certain information regarding the approval of the specific product.²⁷ The first letter of the code indicates whether the Agency has evaluated a particular approved product as therapeutically equivalent to other pharmaceutically equivalent²⁸ products, and the second letter provides additional information regarding the bases of FDA's evaluations.²⁹

Drug products designated with an "A" code fall under one of two main categories. The first category applies to those active ingredients or dosage forms for which no in vivo bioequivalence issue is known or suspected, the information necessary to show bioequivalence between pharmaceutically equivalent products is presumed and considered self-evident based on other data in the application for some dosage forms (e.g., solutions), or is satisfied for solid oral dosage forms by a showing that an acceptable in vitro dissolution standard is met. A therapeutically equivalent rating is assigned such products as long as they are manufactured in accordance with Current Good Manufacturing Practice regulations and meet the other requirements of their approved applications (these are designated AA, AN, AO, AP, or AT, depending on the dosage form). For example, solutions or suspensions in a specific delivery system will be coded "AN" if the bioequivalence standard is based upon in vitro methodology. If bioequivalence for such a solution or suspension needs to be demonstrated by in vivo methodology then the drug products will be coded "AB."³⁰

²⁶ 21 CFR 320.24(a); *Abbreviated New Drug Application Regulations; Proposed Rule*, 54 FR 28872, 28911 (July 10, 1989) ("FDA satisfies [the section 505(j)(7)(A)(i)(III)] requirement through the use of therapeutic equivalence codes" in the Orange Book).

²⁷ Orange Book, Introduction, at xiii.

²⁸ Drug products are considered to be therapeutic equivalents if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. Drug products are considered pharmaceutical equivalents if they have the same active ingredient(s), dosage form, route of administration, and strength or concentration. Id. at vi-vii.

²⁹ Id.

³⁰ Id., at xvi.

The second category of “A” rated drugs relates to post-1962 drug products in a dosage form presenting a potential bioequivalence problem. For such drugs an evaluation of therapeutic equivalence is assigned to pharmaceutical equivalents only if the approved application contains adequate scientific evidence establishing through in vivo and/or in vitro studies the bioequivalence of the product to a selected reference product (these products are designated as “AB”).³¹

Drug products having a “B” as the first letter of their TE code are products that FDA considers not to be therapeutically equivalent to other pharmaceutically equivalent products, and, thus, are drug products for which actual or potential bioequivalence problems have not been resolved by adequate evidence of bioequivalence (designated BC, BD, BE, BN, BP, BR, BS, BT, BX, or B).³² For example, the “BD” code “denotes products containing active ingredients with known bioequivalence problems and for which adequate studies have not been submitted to FDA demonstrating bioequivalence.”³³

II. DISCUSSION

A. Publication of BE Requirements Is not Required within 30 Days of RLD Approval.

You maintain that the FD&C Act required FDA to publish within 30 days of XYREM’s approval on July 17, 2002, whether in vitro, in vivo, or both in vitro and in vivo bioequivalence studies are required for ANDA applicants referencing XYREM, and that FDA’s failure to do so violated the FD&C Act, the Agency’s own regulations, and the Administrative Procedure Act (APA).³⁴ You also maintain that FDA’s acceptance for review, review, or approval of an ANDA referencing XYREM before FDA publishes bioequivalence requirements for XYREM is a violation of the APA, because it constitutes “agency action . . . without observance of procedure required by law,” “not in accordance with law,” “in excess of statutory jurisdiction, authority, or limitations,” and “short of statutory right.”³⁵ You further maintain that if FDA does not publish uniform bioequivalence requirements for all generic sodium oxybate products, and approves multiple generic products with different formulations, products having variable rates and extents of absorption of sodium oxybate would exist. FDA addresses these arguments in turn below.

1. The FD&C Act Does not Require Publication of Bioequivalence Requirements 30 Days after RLD Approval.

³¹ The AB rating is also given for those pre-1962 drug products subject to the Drug Efficacy Study Implementation (DESI) review containing active ingredients or dosage forms that have been identified by FDA as having actual or potential bioequivalence problems that were subsequently resolved through in vivo or in vitro studies. *Id.*, at xiv.

³² *Id.*

³³ *Id.*, at xviii.

³⁴ Petition, at 8.

³⁵ *Id.* (citing 5 USC § 706(2)(A), (C), and (D)).

Your contention that FDA must publish bioequivalence requirements within 30 days of the RLD's approval and listing is unavailing.³⁶ Section 505(j)(7)(A)(i) of the FD&C Act provides that "the Secretary shall publish and make available to the public" three sets of information: "(I) a list in alphabetical order of the official and proprietary name of each drug which has been approved for safety and effectiveness under subsection (c) . . . ; (II) the date of approval if the drug is approved after 1981 and the number of the application which was approved; and (III) whether in vitro or in vivo bioequivalence studies, or both such studies, are required for applications filed under this subsection which will refer to the drug published." The Orange Book lists approved drugs together with the approval date and the application number at the time an NDA is approved, or shortly thereafter. As provided in FDA's bioequivalence regulations as described above, the Agency fulfills the third prong of this statutory directive by including on the list of approved products a "therapeutic equivalence" code for each product once another product that is pharmaceutically equivalent to the listed product is approved. Also as described above, these therapeutic equivalence codes provide details on FDA's determination regarding the bioequivalence data submitted in support of an ANDA.

You contend that section 505(j)(7)(A)(ii), which requires FDA to revise the list every 30 days "to include each drug which has been approved for safety and effectiveness under subsection (c) or approved under this subsection during the thirty day period," also requires FDA to publish the bioequivalence data required in subsection (j)(7)(A)(i)(III) within 30 days of RLD approval.³⁷ This is not clear from the plain language of this provision, however, which only expressly refers to the information regarding the approval of NDAs or ANDAs, and is silent as to when the bioequivalence data requirements must be published. You also assert that the use of the present verb tense in subsection 505(j)(7)(A)(i)(III) (FDA shall publish "whether in vitro, in vivo, or both such studies are required for applications filed under this subsection") requires publication within 30 days of RLD approval.³⁸ Neither of these positions is a supportable interpretation of the requirement, for several reasons.

First, requiring the publication of bioequivalence data type for ANDAs within 30 days of NDA approval would be inconsistent with several provisions of the statute and FDA's regulations. For example, section 505(j)(3)(B) requires the Agency to meet with an ANDA applicant to agree on the design and size of bioequivalence studies needed for approval if an applicant submits a reasonable written request for such a meeting. Under your view, the bioequivalence method would have been determined and published when FDA first approved and listed the RLD, and there would be no reason for such meetings with ANDA applicants. You assert that this section is not inconsistent with your position because "a determination whether in vitro or in vivo studies are required does not determine the design and size of the studies."³⁹ This position fails to understand the nature of bioequivalence methodologies, in which the type of data required to

³⁶ Petition, at 8, 12-13.

³⁷ Petition, at 11.

³⁸ Id.

³⁹ Id., at 12.

demonstrate bioequivalence (in vivo, in vitro, etc.) is not segregable from the design and size of such studies. As reflected in 21 CFR 320.24(b)(1)-(6), the acceptability of a particular type of bioequivalence data is tied to the sufficiency of trial design.⁴⁰

Second, your position is infeasible as a practical matter, because it would require the Agency to generate and evaluate the scientific data required to determine bioequivalence requirements *at the time the RLD is listed*, without the benefit of any insight into the characteristics of the RLD that marketing experience with the drug might provide. Your argument that FDA need not expend resources to determine the type of bioequivalence data required for a product⁴¹ fails to recognize that a determination of the appropriate bioequivalence methodology must be supported by scientific evidence. As described in the guidance for industry on *Bioequivalence Recommendations for Specific Products* (June 2010), the Agency expends many resources developing bioequivalence recommendations “based on its understanding of the characteristics of the listed drug, information derived from published literature, Agency research, and consultations within different offices CDER as needed based upon the novelty or complexity of the BE considerations.”⁴² FDA also accepts alternative data and methods proposed by individual ANDA applicants as long as that data meets the statutory requirements for approval. Notably, little if any of this information would be available at the time of RLD listing.

Your position also fails to recognize that there are many products approved under NDAs for which generic versions are never sought, or are sought only after science has developed acceptable bioequivalence methodologies. Your position would nonetheless require FDA to determine bioequivalence methodologies for these products at the time the RLD is approved. This is impracticable, and would result in a waste of agency resources. FDA’s approach, by contrast, permits the Agency, and by extension, the public health, to benefit from knowledge gained from the use of the RLD post-approval and from scientific developments more generally prior to determining appropriate bioequivalence methodologies.

Third, there is no indication that Congress intended to place such a burden on the Agency through subsection 505(j)(7)(A)(i)(III). Nor have any of the courts that have considered FDA’s compliance with section 505(j)(7)(A)(i)(III) construed the statute in the manner you suggest, or otherwise have found any legal deficiency in FDA’s practice of listing bioequivalence data requirements for a listed drug at the time a pharmaceutically equivalent drug is approved.⁴³

⁴⁰ Similarly, your reference to the fact that the therapeutic equivalence codes in the Orange Book do not reflect the study and design of data is unavailing. Petition, at 12. That FDA did not list study design does not mean the agency did not consider study design when determining the acceptability of bioequivalence data.

⁴¹ Petition, at 13.

⁴² *Bioequivalence Recommendations for Specific Products*, at 2.

⁴³ See, e.g., *Schering Corp. v. FDA*, 51 F.3d at 398 (citing section 505(j)(7)(A)(i)(III)) as evidence of Congressional intent to provide FDA discretion to determine appropriate bioequivalence methodology through the course of the ANDA approval process). You assert that the *Schering* decision did not address whether FDA is required to publish bioequivalence data requirements at the time of RLD listing and

Finally, there is no indication that FDA's current interpretation of the requirement of subsection 505(j)(7)(A)(i)(III) prejudices the entities for which such information is intended to benefit, namely, the ANDA sponsors. FDA has many mechanisms through which information regarding appropriate bioequivalence methods can be gained prior to approval of the first therapeutically equivalent product, including consultation with the Agency, which is expressly encouraged in FDA's regulations.⁴⁴ In addition, FDA has issued numerous guidances on demonstrating bioequivalence for classes of products,⁴⁵ and has issued over 1020 product-specific bioequivalence guidances, which provide FDA's recommended approach for demonstrating bioequivalence for particular products.⁴⁶ FDA further notes that TE codes themselves indicate to subsequent applicants what FDA accepted (or did not accept) for the first therapeutically equivalent product referencing an RLD. Publication of the type of data FDA accepted for an ANDA referencing an RLD at the time of approval of the ANDA retains maximum flexibility for ANDA applicants to demonstrate bioequivalence in accordance with the statute and regulations. Requiring FDA to publish bioequivalence requirements at the time of RLD listing would extinguish that flexibility to great harm to the ANDA applicant and to the public health, which benefits from the availability of generic products that are approved using the most appropriate bioequivalence methodologies.

2. FDA Is not Required to Publish Bioequivalence Recommendations Prior to Acceptance, Review, or Approval of an ANDA.

You next assert that FDA's acceptance for review, review, or approval of an ANDA referencing XYREM before the Agency has published bioequivalence requirements violates the APA.⁴⁷ Refusing to accept for review, review or approve an ANDA on these grounds would conflict directly with several provisions of the FD&C Act and FDA regulations. Subsection 505(j)(2)(A) of the FD&C Act delineates what information is required in an ANDA, and expressly states that FDA "may not require that an abbreviated application contain information in addition to that required by clauses (i) through (viii)."⁴⁸ Subsection 505(j)(2)(A)(iv) in particular requires "information show that

therefore does not support FDA's position. Petition, at 12. A fundamental component of the court's decision, however, is the conclusion that FDA has the discretion to determine appropriate bioequivalence methodology on "a case-by-case basis depending on the drug under consideration for approval pursuant to an ANDA." Id. at 399. Your theory that bioequivalence methods for all ANDAs referencing an RLD must be determined at the time of RLD listing is inconsistent with this product-by-product approach.

⁴⁴ 21 CFR 320.30 (Inquiries regarding bioavailability and bioequivalence requirements and review of protocols by the Food and Drug Administration) ("[t]he Commissioner of Food and Drugs strongly recommends that, to avoid the conduct of an improper study and unnecessary human research, any person planning to conduct a bioavailability or bioequivalence study submit the proposed protocol for the study to FDA for review prior to the initiation of the study").

⁴⁵ See, e.g., BA/BE Guidance, draft guidance for industry on *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* (April 2003).

⁴⁶ Guidance for industry on *Bioequivalence Recommendations for Specific Products* (Aug. 2010). This and the product-specific bioequivalence recommendation guidances are available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm>.

⁴⁷ Petition, at 8.

⁴⁸ Section 505(j)(2)(A) of the FD&C Act.

the new drug is bioequivalent to” to the RLD, and does not reference the bioequivalence information listing requirement that you assert must be completed by FDA to permit FDA’s review of an ANDA. Likewise, 21 CFR 314.101 of FDA’s regulations sets out the bases on which FDA may or will receive (or refuse to receive) an ANDA for substantive review, and failure of FDA to publish bioequivalence information is not one of the bases for FDA to refuse to receive an application. In fact, FDA’s refusal to receive an application on the ground that FDA had not yet published the information required by subsection 505(j)(7)(A)(i)(III) would directly conflict with these statutory and regulatory provisions.

With regards to review and approval of an ANDA, FDA decides whether to approve an application based on the Agency’s evaluation of the scientific information provided in the application, under the requirements of the FD&C Act and regulations, and in reliance on the Agency’s scientific experience and judgment. If an applicant complies with all applicable statutory requirements, subsection 505(j)(4) of the FD&C Act directs that the Agency “shall approve” the application, unless one of the delineated bases for not approving a product exists. With respect to bioequivalence, subsection 505(j)(4)(F) provides that an ANDA is not approvable if the information submitted in the application “is insufficient to show that the drug is bioequivalent” to the RLD. There is no mention of refusal to approve on the ground that the Agency failed to publish applicable bioequivalence requirements.⁴⁹ The Agency’s delay or denial of an ANDA’s approval based on a failure to publish bioequivalence requirements in the Orange Book thus would be inconsistent with this provision of the FD&C Act as well.⁵⁰ In addition, as courts have uniformly endorsed, the FD&C Act gives FDA broad discretion to determine how bioequivalence must be demonstrated for a generic product.⁵¹ Your proposed interpretation of section 505(j)(7)(A)(i) to prohibit FDA’s acceptance for review, review, or approval of ANDAs referencing XYREM before publication of bioequivalence requirements is inconsistent with this broad discretion.

It is also critical to recognize that the remedy you propose is fundamentally inconsistent with the purpose of section 505(j)(7)(A)(i)(III) itself. The purpose of listing

⁴⁹ Section 505(j)(4) of the FD&C Act.

⁵⁰ See Letter from Dr. Janet Woodcock, Director, Center for Drug Evaluation and Research, FDA, to Mr. Izumi Hara, Warner Chilcott Company, LLC, and Dr. Jeffrey Jonas, Shire Pharmaceuticals, Inc., re: Docket Nos. 2010-P-0111 and 2008-P-0507 at 14.

⁵¹ The Third Circuit, in upholding FDA’s “method to determine bioequivalence on a case-by-case basis depending on the drug under consideration for approval pursuant to an ANDA,” concluded after detailed review of the legislative history and Agency rulemaking that “there is no evidence that Congress intended to limit the discretion of the FDA in determining when drugs were bioequivalent for the purposes of ANDA approval.” *Schering Corp. v. FDA*, 51 F.3d at 399. See also *Bristol-Myers Squibb v. Shalala*, 923 F. Supp. 212, 217 (D.D.C. 1996) (“the expressed desire of Congress, through the 1984 amendments, was that FDA retain its historically wide discretion in defining showings of bioequivalence”) (internal citation and quotation omitted); *Fisons Corp v. Shalala*, 860 F. Supp. at 866-67 (“[T]he factual determination of how bioequivalence is determined properly rests within the FDA’s discretion”); *Astellas Pharma US, Inc., v. FDA*, 642 F. Supp. 2d 10, 19 (D.D.C. 2009) (the “high degree of deference” given to FDA’s scientific determinations “has been applied to the FDA’s determinations regarding which methodologies it determines are needed to test the bioequivalency of a given generic”).

bioequivalence data requirements is, as you agree,⁵² to benefit ANDA applicants by providing them with information to assist in developing generic products. It is not reasonable to interpret section 505(j)(7)(A)(i) to punish ANDA applicants that otherwise meet the requirements for submission, review or approval due to any alleged failure on FDA's part to publish the required information.⁵³ The only parties who stand to benefit from a delay in accepting, reviewing and/or approving products on the ground that FDA has not published bioequivalence requirements are not ANDA applicants, but rather RLD sponsors who will benefit from a delay in generic competition in the marketplace. It would, thus, turn section 505(j)(7)(A)(i)(III) on its head to interpret it in the manner you propose

3. FDA May Accept Different Bioequivalence Data for ANDAs Referencing the Same RLD.

Third, we are not persuaded by your contention that the same bioequivalence requirements must be met by all generic sodium oxybate products, and that if FDA does not publish uniform bioequivalence requirements for all generic sodium oxybate products, and approves multiple generic products with different formulations, products having variable rates and extents of absorption of sodium oxybate would exist.⁵⁴

As discussed more fully below, formulation differences from the RLD are permitted in generic products but are closely evaluated during ANDA review to determine whether the differences would affect the absorption of the active ingredient or moiety. FDA may require ANDA applicants to conduct in vivo bioequivalence studies if the Agency determines that formulation differences may affect absorption, and the Agency would not approve an ANDA in such cases absent a demonstration of bioequivalence.

More generally, your position is inconsistent with FDA's bioequivalence regulations. Subsection 320.24(a) provides that "[t]he selection of the method used to meet an in vivo or in vitro testing requirement depends upon the purpose of the study, the analytical methods available, and the nature of the drug product." This regulation requires applicants to "conduct bioavailability and bioequivalence testing using the most accurate, sensitive, and reproducible approach available among those set forth in paragraph (b) of this section." Limiting FDA to accepting one type of bioequivalence study for all ANDAs referencing the same RLD regardless of the characteristics of the proposed products and requiring FDA to choose that methodology within 30 days of the RLD's approval could result in ANDA approvals that are directly inconsistent with this regulatory directive. For example, regulatory science has made significant advances with respect to the type of data available to demonstrate bioequivalence for a variety of

⁵² Petition, at 13.

⁵³ See also *Teva Pharms., USA, Inc. v. Leavitt*, 548 F.3d 103, 301 (2008) (holding that a patent certification was improper after the RLD holder delisted the relevant patent notwithstanding that FDA had not yet revised the printed Orange Book to reflect the delisting, and concluding that "[i]nadvertent failure by the agency to meet its separate publication requirement" cannot affect ANDA applicant's substantive rights and responsibilities).

⁵⁴ Petition, at 9-10, 22-23.

products for which comparative clinical endpoint studies were once recommended.⁵⁵ Your interpretation effectively would limit FDA to accepting only the type of bioequivalence data available at the time the RLD was listed in the Orange Book. It thus would preclude FDA from accepting new, scientifically innovative study designs notwithstanding the fact that data generated using such study designs were more sensitive, accurate, and reproducible than those generated using previously accepted study designs.⁵⁶

In addition, FDA has exercised, and courts have upheld, the Agency's discretion to accept different bioequivalence methodologies for different ANDAs that reference the same RLD depending on differences between the proposed products. For example, FDA has determined under 21 CFR 320.24(a) that certain proposed products that have qualitatively (Q1) and quantitatively (Q2) the same inactive ingredients as the RLD can be supported by in vitro data to demonstrate bioequivalence, but that comparative clinical trials may be the most sensitive, accurate, and reproducible for certain other proposed products that do not share the same inactive ingredient profile as the RLD.⁵⁷ Courts also have upheld FDA's discretion to modify the data the Agency accepts to demonstrate bioequivalence as scientific advances develop.⁵⁸ Finally, to the extent that information available at the time the RLD is approved only supports use of in vivo data, but science subsequently advances to support use of in vitro data, requiring ANDA applicants to use in vivo data because that was the best method available at the time the RLD was approved also runs counter to the important public health policy recognized in FDA's bioequivalence regulations that no unnecessary human research should be conducted.⁵⁹

⁵⁵ See e.g., Aug. 20, 2010, Letter fr. FDA to I.Hara, Warner Chilcott Co. LLC, at 11 (concluding comparative clinical endpoint studies "less sensitive, accurate, and reproducible" than in vitro dissolution and pharmacokinetic studies for mesalamine, a locally acting GI product); See generally, guidance for industry *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System* (Aug. 2000) (BCS Guidance).

⁵⁶ *ViroPharma, Inc. v. Hamburg*, No. 12-0584, 2012 U.S. Dist. LEXIS 56128, at *58 (D.D.C. April 23, 2012) (upholding FDA's authority to accept in vitro data in support of demonstrating bioequivalence in lieu of prior recommendation to submit in vivo data from clinical endpoint studies); *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. at 218.

⁵⁷ See April 9, 2012, Letter fr. FDA to T. Doyle, at 20-21 (affirming in vivo clinical endpoint studies are required for non-Q1/Q2 generic vancomycin hydrochloride capsules unless applicant can demonstrate formulation differences do not affect safety or effectiveness of product). See also Dec. 8, 2010, Letter fr. FDA to J. Jonas, Shire Development Inc., at 6-7 (denying request to require clinical efficacy studies to demonstrate bioequivalence for locally acting lanthanum carbonate oral chewable tablets, concluding that "comparative in vivo trials would be less sensitive, accurate or reproducible than [pharmacodynamics] or properly designed and conducted in vitro dissolution and binding studies with respect to the capability to detect product differences"); Draft Guidance on *Acarbose*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM170242.pdf>.

⁵⁸ *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. at 218 (citing section 505(j)(7)(A)(i)(III)) in support of holding that FDA has authority to change bioequivalence recommendation to accept in vitro data rather than formerly recommended in vivo and in vitro data)

⁵⁹ 21 CFR 320.25(a). See also 21 CFR 320.30(a) ("[t]he Commissioner of Food and Drugs strongly recommends that, to avoid the conduct of an improper study and unnecessary human research, any person

In sum, FDA's interpretation of the requirement of section 505(j)(7)(A)(i)(III) is reasonable, gives effect to (and does not abrogate) other provisions of section 505(j), does not impose on the Agency the onerous burden of determining bioequivalence requirements at the time of RLD approval without input from generic applicants and without the benefit of marketing experience with the drug. It also furthers the significant public health policies of encouraging innovation and reducing unnecessary human testing. Your interpretation of the FD&C Act, the Agency's regulations, and the APA, which would require FDA to publish bioequivalence requirements at the time of RLD approval and apply those requirements to all ANDA applicants regardless of advances in science or changes in understanding of relevant characteristics of the RLD, is not consistent with any of these outcomes. Your requests are therefore denied.

B. Therapeutic Equivalence Evaluations

You next maintain that FDA's publication of TE codes in the Orange Book upon approval of an ANDA does not adequately fulfill the Agency's obligation to publish bioequivalence requirements for approved RLDs because the TE codes do not constitute legal requirements, and their publication therefore cannot constitute publication of bioequivalence requirements for the purposes of subsection 505(j)(7)(A)(i)(III).⁶⁰ In support of this argument, you cite FDA's statement in the preface to the Orange Book that "[t]herapeutic equivalence evaluations in this publication are not official FDA actions affecting the legal status of products under the Act."⁶¹ You take this statement out of context, however.

As explained in detail in the Orange Book introduction section expressly addressing "General Policies and Legal Status":

The List contains public information and advice. It does not mandate the drug products which is purchased, prescribed, dispensed, or substituted for one another, nor does it, conversely, mandate the products that should be avoided. To the extent that the List sets forth FDA's evaluations of the therapeutic equivalence of drug products that have been approved, it contains FDA's advice to the public, to practitioners and to the states regarding drug product selection. These evaluations do not constitute determinations that any product is in violation of the Act or that any product is preferable to any other. Therapeutic equivalence evaluations are a scientific judgment based upon evidence, while generic substitution may involve social and economic policy administered by the states, intended to reduce the cost of drugs to consumers. *To the extent that the List identifies drug products approved under Section 505 of the Act, it sets forth information that the Agency is required to publish and that the public is entitled to under the Freedom of Information Act.* Exclusion of a drug product from the List does not necessarily mean that the drug product is either in violation of

planning to conduct a bioavailability or bioequivalence study submit the proposed protocol for the study to FDA for review prior to the initiation of the study").

⁶⁰ Petition, at 10.

⁶¹ Petition, at 10.

Section 505 of the Act, or that such a product is not safe or effective, or that such a product is not therapeutically equivalent to other drug products. Rather, the exclusion is based on the fact that FDA has not evaluated the safety, effectiveness, and quality of the drug product.⁶²

Accordingly, FDA's statement in the Orange Book preface you cite simply advised against interpretation of TE codes for purposes other than indicating FDA's scientific determinations concerning the bioequivalence and the therapeutic equivalence of drug products that have been approved. It did not indicate that TE codes could not be used to convey the information required in section 505(j)(7)(A)(i). Indeed, FDA expressly indicates that the list reflects information the agency is legally required to publish.

C. Requirement for In Vitro, In Vivo, or both In Vitro and In Vivo BE Studies

You next assert that under the FD&C Act, FDA must require ANDA applicants to conduct in vitro, in vivo, or both in vitro and in vivo studies to establish bioequivalence to an RLD, and FDA, therefore, cannot permissibly waive both in vitro and in vivo bioequivalence studies for an ANDA applicant.⁶³

As discussed above in section I.B, FDA has considerable discretion to determine the most appropriate bioequivalence methodology for each product it approves. In 21 CFR 320.22 of FDA's bioequivalence regulations, the Agency has identified types of drug products for which the in vivo bioequivalence of a drug product to be self-evident, and provides a mechanism by which an applicant may seek a waiver of an in vivo bioequivalence requirement imposed by the Agency.⁶⁴ Specifically, if FDA determines that in vivo data are the appropriate means of demonstrating bioequivalence for a product, ANDA applicants may apply for a waiver of such in vivo bioequivalence requirement if the product is in one of the identified classes for which bioequivalence may be considered self-evident and meets certain additional criteria.⁶⁵ For oral solutions, the regulations provide for a waiver of an in vivo bioequivalence requirement if an ANDA applicant demonstrates that its individual product contains the same active ingredient in the same concentration as the RLD and that it contains no inactive ingredient or other change in formulation from that of the RLD that may significantly affect absorption of the active ingredient or moiety.⁶⁶

⁶² Orange Book, Introduction, at iv (emphasis added).

⁶³ Petition, at 14.

⁶⁴ 21 CFR 320.22.

⁶⁵ 21 CFR 320.21(t) ("Information to permit FDA to waive the submission of evidence measuring the in vivo bioavailability or demonstrating the in vivo bioequivalence shall meet the criteria set forth in 320.22").

⁶⁶ 21 CFR 320.22(b)(3). See also BA/BE Guidance, at 12. ("[g]enerally, in vivo BE studies are waived for solutions on the assumption that release of the drug substance from the drug product is self-evident and that the solutions do not contain any excipient that significantly affects drug absorption (21 CFR 320.22(b)(3)(iii))." See generally, 21 CFR 320.22(b)-(d) (additional categories of products for which waivers of an in vivo data requirement may be sought).

Accordingly, if FDA determines that in vivo bioequivalence data are necessary for generic sodium oxybate products, FDA may waive such requirement if the applicant demonstrates that its individual product contains the same active ingredient in the same concentration and dosage form as XYREM, and contains no inactive ingredient or other change in formulation from that of XYREM that may significantly affect absorption of the active ingredient.⁶⁷ If the Agency were to waive a requirement for in vivo bioequivalence data for an ANDA applicant that meets the criteria under subsection 320.22(d)(3), the applicant would be deemed to have complied with and fulfilled the requirement for in vivo bioequivalence data. Because the applicant would be considered to have met the requirement for a demonstration of in vivo bioequivalence, the Agency could permissibly approve the ANDA without requiring in vitro bioequivalence data. As FDA discussed in proposing subsection 320.22 waivers in the bioequivalence context:

In some cases, the in vivo bioavailability of a drug product may be self-evident, e.g., for a drug product that is a solution intended for intravenous or oral administration. . . . The agency does not believe Congress intended that unnecessary human research be conducted in cases where an applicant could demonstrate that a product is inherently bioequivalent to another product and therefore meets the statutory standard of bioequivalence. Therefore, the agency proposes to continue its policy that if an applicant can demonstrate that its proposed drug product falls in this category, *such a demonstration would be considered adequate information to show bioequivalence* to the reference listed drug, as required in proposed § 314.94(a)(7)(i).⁶⁸

Your request that FDA require any ANDA applicant for which an in vivo bioequivalence data requirement is waived to submit in vitro data is accordingly denied as inconsistent with FDA's regulations.

D. Bioequivalence Requirements for ANDAs referencing XYREM

You maintain that in vivo bioequivalence studies should only be waived for ANDA applicants referencing XYREM if a proposed product's formulation does not differ from XYREM's in terms of its pH, excipients, impurities, degradants, or contaminants, and if the product is produced using the same manufacturing process as is used for XYREM.⁶⁹ You also state that if the formulation proposed in an ANDA application referencing XYREM differs from XYREM's formulation, the applicant should be required to either submit in vivo bioequivalence studies or data demonstrating that the formulation differences do not significantly affect absorption of the sodium oxybate (the latter of which, you

⁶⁷ As noted above, notwithstanding the fact that an applicant meets these criteria, FDA does retain the ultimate authority to require in vivo bioequivalence data if the Agency determines that any difference between the drug product and a listed drug may affect the bioequivalence of the drug product. 21 CFR 320.22(f).

⁶⁸ ANDA Proposed Rule, 54 Fed. Reg., at 28,883 (emphasis added).

⁶⁹ Petition, at 14-16.

assert, are unavailable).⁷⁰ You state that formulation and manufacturing process differences may result in levels of GBL in proposed generic products that differ from the level in XYREM and that such differences would affect the rate and extent of absorption and onset of action of sodium oxybate in the proposed generic products, potentially resulting in pharmacokinetic and pharmacodynamic differences, and possibly affecting the proposed products' safety and effectiveness.⁷¹ Finally, you argue that these differences may be compounded by the role that monocarboxylic acid transporters (MCTs) play in the absorption of GHB.

Your assertions are unavailing. First, you assert that Xyrem's manufacturing process together with rigorous quality control standards that include tight specifications for overall purity of the GBL starting material and the product's final pH ensure its stability over the shelf life of the product. You contend that a generic product with a different manufacturing process and formulation would not be able to similarly ensure such characteristics in the absence of in vivo bioequivalence data.⁷² This position is unavailing. During ANDA review, detailed information about the manufacturing process, pH, excipients, impurities, degradants, and contaminants for the proposed generic product must be submitted in the ANDA, and is carefully reviewed by Agency staff.⁷³ Specification limits for the pH range and levels of impurities, degradants, and contaminants must be proposed by the ANDA applicant,⁷⁴ and levels of impurities, degradants, and contaminants (including GBL) in the proposed generic product must be controlled for and qualified.

For example, FDA's guidance for industry *ANDAs: Impurities in Drug Products* sets forth the Agency's recommendations on what chemistry, manufacturing, and controls (CMC) information sponsors should include regarding the reporting, identification, and qualification of impurities that are classified as degradation products in drug products when submitting an ANDA.⁷⁵ The guidance also provides recommendations for establishing acceptance criteria for degradation products (specifically, degradation products of the active ingredient or reaction products of the active ingredient with an excipient(s) and/or immediate container/closure system) in generic drug products.⁷⁶ FDA also reviews the manufacturing process of the generic product to confirm, among other things, that there are adequate validated controls in place to assure that a generic product

⁷⁰ Id., at 15-16.

⁷¹ Id., at 17.

⁷² Id., at 15-16.

⁷³ 21 CFR 314.94(a)(2)(i) (requiring ANDA applicants to submit the detailed chemistry, manufacturing and controls information required by NDA applicants with limited exception regarding the proposed drug product and drug substance contained therein).

⁷⁴ 21 CFR 314.94(a)(2)(ii) ([u]nless otherwise stated in paragraphs (a)(9)(iii) through (a)(9)(v) of this section, an applicant shall identify and characterize the inactive ingredients in the proposed drug product and provide information demonstrating that such inactive ingredients do not affect the safety or efficacy of the proposed drug product).

⁷⁵ Guidance for industry on *ANDAs: Impurities in Drug Products*, at 1 (Nov. 2010), available on the Internet at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

⁷⁶ Id.

will meet the specifications set out in the ANDA. Accordingly, although a generic sodium oxybate product may differ in formulation from Xyrem, FDA's review will assure that the generic product also includes tight specifications for overall purity of the GBL starting material and the product's final pH that ensure its stability over the shelf life of the product.

In addition, differences in manufacturing processes, pH, excipients, impurities, degradants, or contaminants between generic products and the RLD are closely evaluated during ANDA review to determine whether such differences would affect absorption of the active ingredient or moiety and/or the safety and efficacy of the proposed product. As described in section I.B, above, if the differences are determined not to affect absorption, safety, or efficacy, a waiver of an in vivo bioequivalence requirement may be granted. If differences exist that may affect absorption or safety and effectiveness, FDA may then require in vivo studies if the agency determines that data from such studies are necessary demonstrate bioequivalence.⁷⁷ You have not provided any evidence why this review process would be insufficient to identify and address differences in formulation such that FDA should require in vivo bioequivalence data for all generic sodium oxybate products that differ in formulation or manufacturing process in the first instance.

Second, FDA does not share your concern that differences in levels of GBL, present either in the drug product as a manufacturing contaminant or as a byproduct of a pH-dependent degradation reaction may affect active transport of sodium oxybate (GHB) via drug transporters.⁷⁸ GHB and GBL are subject to interconversion in aqueous solution by a pH-dependent process, meaning that it is only under certain pH conditions that GBL will convert to GHB. As described above, specification limits for both GBL levels and pH range of a proposed generic product would be reviewed by FDA to ensure that they are controlled for and within acceptable limits. You have offered no evidence that these specification and controls requirements will not ensure acceptable GBL levels in a generic product.

Third, you argue that in vivo bioequivalence data is critical for generic sodium oxybate products due to the important role that drug transporters like MCTs play. The MCTs are transport proteins that are involved in the absorption, renal clearance, and distribution of certain compounds including GHB throughout the body.⁷⁹ Upon review of the literature you cite, FDA finds that your assertions regarding the potential involvement of MCTs in the absorption of GHB are based on published reports of nonclinical (in vitro and animal) studies. You did not provide evidence to show that a correlation exists between the in vitro and/or animal data and human data on GHB absorption. Your argument therefore is

⁷⁷ For example, as FDA discussed in the BA/BE Guidance, certain excipients, such as sorbitol or mannitol, can reduce the bioavailability of drugs with low intestinal permeability in amounts sometimes used in oral liquid dosage forms. BA/BE Guidance, at 18. If such excipients were present in an oral solution for a product with low intestinal permeability, FDA carefully would evaluate whether the excipient's presence in that particular drug product would affect absorption, safety and/or effectiveness and if so, FDA may require in vivo bioequivalence data.

⁷⁸ Petition, at 17.

⁷⁹ Petition, at 19.

unsupported.

In addition, FDA has concluded that certain in vitro studies of the effect of MCTs on GHB absorption have called into question the clinical importance of transporter-mediated GHB uptake. As a general matter, Biopharmaceutics Classification System (BCS) Class 1 compounds, which by definition have high intestinal permeability and are highly soluble, are well-absorbed through the intestines.⁸⁰ Although BCS Class I compounds may be substrates for uptake or efflux transporters in in vitro cellular systems under certain conditions, intestinal uptake of such compounds via transporters does not play an important role in absorption due to their rapid intestinal permeation.⁸¹ The effect of MCTs on the absorption of highly soluble and permeable compounds is therefore not clinically significant in the manner you suggest.

This observation is relevant because GHB is highly soluble and has been shown to have moderate to high intestinal permeability⁸² in an in vitro cellular system.⁸³ Therefore, GHB would be expected to be well-absorbed through the intestines, and the clinical significance of MCT-mediated uptake of GHB is likely marginal at best. Contrary to your assertions,⁸⁴ the action of MCTs would therefore likely have little impact on whether generic sodium oxybate formulations that differ from XYREM in manufacturing process, pH, excipients, degradants, or contaminants would result in different therapeutic concentrations of the drug.

Fourth, you maintain that food significantly affects the absorption, onset of action, and bioavailability of XYREM due to MCT-mediated intestinal uptake of GHB, and that ANDA applicants required to conduct in vivo bioequivalence studies should therefore be required to conduct the studies under both fed and fasted conditions.⁸⁵ As a preliminary matter, we agree that food affects the bioavailability of sodium oxybate, but your contention that this effect is due to the actions of MCTs is unpersuasive for the reasons discussed above.

With respect to whether the FDA would require a fed study as part of any in vivo bioequivalence requirement, as noted in section I.D. above, FDA expects ANDA applicants for orally administered drug products to conduct bioequivalence studies under fed and fasted conditions unless certain exceptions apply. The circumstances in which bioequivalence studies under fed conditions are not recommended include when the

⁸⁰ Draft Guidance for Industry *Drug Interaction Studies - Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*, February, 2012, available on the Internet at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

⁸¹ Custodio JM, Wu CY, Benet LZ. Predicting drug disposition, absorption/elimination/transporter interplay and the role of food on drug absorption, *Adv Drug Deliv Rev.*, 2008.

⁸² Lam WK, Felmlee MA, Morris ME. Monocarboxylate transporter-mediated transport of gamma-hydroxybutyric acid in human intestinal Caco-2 cells. *Drug Metab and Dispos.* 2011.

⁸³ D.A.Volpe, P.J.Faustino, A.B.Ciavarella, E.B.Asafu-Adjaye, C.C.Ellison, L.X.Yu, and A.S.Hussain. Classification of drug permeability with a Caco-2 cell monolayer assay, *Clinical Research and Regulatory Affaires*, 24(1): 39-47. 2007.

⁸⁴ Petition, at 19-20.

⁸⁵ Petition, at 20-21.

RLD labeling states that the product should be taken only on an empty stomach; or when both the ANDA and the RLD are rapidly dissolving, have similar dissolution profiles, and contain a drug substance with high solubility and high permeability. XYREM satisfies the first of these exceptions because the DOSAGE AND ADMINISTRATION section of the XYREM labeling states that “[b]ecause food significantly reduces the bioavailability of sodium oxybate, the patient should allow at least 2 hours after eating before taking the first doses of sodium oxybate. Patients should try to minimize variability in the timing of dosing in relation to meals.”⁸⁶ Xyrem may also meet the second exception, but FDA has not yet made a Biopharmaceutics Classification System determination for the product. Accordingly, in the absence of further guidance from the Agency, if FDA were to require an ANDA applicant referencing XYREM to conduct in vivo BE studies, the applicant would be expected to conduct the studies only under fasted conditions.

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 stylized flourish at the end.

Janet Woodcock, M.D.

Director

Center for Drug Evaluation and Research

⁸⁶ Xyrem Package Insert, at 13.