January 12, 2017

Electronically Filed

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

Re: Response to Docket No. FDA-2016-P-2672-0017

On September 2, 2016, Jazz Pharmaceuticals, Inc. (Jazz) submitted a citizen petition requesting that FDA refuse to approve any ANDA referencing Xyrem® (sodium oxybate) oral solution that purports to omit information regarding the drug-drug interaction (DDI) between sodium oxybate and divalproex sodium (divalproex) from the labeling for the proposed generic drug. Jazz also requested that FDA refuse to approve any ANDA referencing Xyrem that fails to contain the aspects of the approved risk evaluation and mitigation strategy (REMS) for Xyrem pertaining to divalproex. Omitting information regarding the divalproex DDI from the labeling for generic sodium oxybate would result in generic products that are less safe and effective than Xyrem in violation of 21 C.F.R. § 314.127(a)(7).[1] Omitting the REMS aspects related to the divalproex DDI would also violate 21 U.S.C. § 355-1(i)(1)(B).[2]

Par Pharmaceutical, Inc. (Par) has submitted comments opposing the Petition, principally arguing that the divalproex DDI does not present a real safety concern and that the dosing and monitoring instructions and other information related to that DDI may be freely omitted from the labeling and REMS for generic sodium oxybate.[3] Par's arguments are meritless. As Jazz explains in detail below, the potential interaction between divalproex and sodium oxybate is obviously a genuine safety risk. Omitting information related to that

[1] Citizen Petition, Docket No. FDA-2016-P-2672-001, 9-13 (Sept. 2, 2016) (Petition).

[2] *Id.* at 13-14.

[3] *See generally* Comment, Docket No. FDA-2016-P-2672-0017 (Nov. 15, 2016) (Par Comment). Par also makes a variety of unfounded accusations regarding allegedly "anti-competitive" conduct by Jazz relating to Jazz's patents covering the information related to the divalproex DDI. *See, e.g.*, *id.* at 1, 3, 17. In general, Jazz will not respond to Par's accusations in this submission as they are neither within FDA's jurisdiction nor relevant to the issues at hand. *See, e.g.*, Citizen Petition Response, Docket No. FDA-2010-P-0614, 26 (May 25, 2011) (Colcrys Response) ("assertions regarding anti-competitive conduct . . . are not within the province of FDA"). Suffice it to say that seeking a patent to protect a valuable discovery is not "anti-competitive." Rather, patents "promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries." U.S. Constitution, Art. I, § 8, cl. 8. In this case, the U.S. Patent Office determined that Jazz's discoveries regarding the DDI between sodium oxybate and divalproex are worthy of protection. *See* U.S. Patent Nos. 8,772,306 and 9,050,302; *see also* 35 U.S.C. § 282(a) ("A patent shall be presumed valid."). Moreover, that determination was upheld by the U.S. Patent and Trademark Appeals Board (PTAB) when it soundly rejected Par's attempt to invalidate the '306 patent through *inter partes* review. *See Par Pharm., Inc. v. Jazz Pharms. Ireland Ltd.*, Case IPR2016-00002, Paper No. 12 (P.T.A.B. Apr. 12, 2016).

risk from the labeling for generic sodium oxybate will necessarily result in a less safe and less efficacious product, in violation of FDA's regulations. Further, omitting aspects designed to mitigate that risk from a REMS for generic sodium oxybate would not be comparable to the Xyrem REMS Program, in violation of the FDCA. For the reasons discussed below, and those previously stated, Jazz's citizen petition should be granted.

I. The Drug-Drug Interaction Between Sodium Oxybate And Divalproex Presents A Genuine Safety Issue.

Par's main argument in favor of omitting information related to the divalproex DDI from the labeling and REMS of generic sodium oxybate is that the DDI between sodium oxybate and divalproex does not present a "concrete safety risk to patients."[4] Par similarly claims that the dosing instructions and screening measures related to divalproex in the approved labeling and REMS for Xyrem do not constitute "a significant safety measure."[5] Par goes so far as to assert that the risk associated with the interaction between sodium oxybate and divalproex "Does Not Exist in . . . Clinical Practice"[6] and lacks "any connection to the actual Xyrem patient population."[7]

These assertions are utterly without merit. As an initial matter, Par's current claim that the safety concerns presented by the DDI between sodium oxybate and divalproex are merely "theoretical"[8] is contrary to the position that Par took before the PTAB—there, Par's position was that the risk of excessive sodium oxybate exposure when the two drugs are administered concomitantly is "high."[9] Moreover, Par's current position is not even internally consistent. At the same time Par contends that the divalproex DDI poses only theoretical safety concerns, Par proposes to modify the labeling for its generic sodium oxybate to instruct providers "not to administer the two drugs together."[10] Under applicable law, Par's proposal to include a contraindication necessarily presumes that the divalproex DDI poses a genuine and serious safety concern.[11]

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[4] Par Comment at 5.

[5] *Id.*

[6] *Id.* at 6

[7] *Id.* at 8.

[8] *Id.* at 2.

[9] *See* Petition, Exhibit 1 at 25 ("[R]ecognizing that there may also be a potential pharmacokinetic interaction [with divalproex] that could elevate GHB concentrations in the brain, a [presciber] would consider reducing the dose further, as the risk of excessive dosing of a patient with GHB is high . . . .") (emphasis in the original); *see also id.* at 27 ("[T]he principle would have been to 'start low and go slow,' especially since the risk of underdosing GHB (a reduction in efficacy) is minimal, but the risk of excessive dosing is high.").

[10] Par Comment at 8 (emphasis in the original).

[11] *See* 21 C.F.R. § 201.57(b)(5) (a contraindication means that "the risk of use (e.g., certain potentially fatal adverse reactions) clearly outweighs any possible therapeutic benefit"); *see also* FDA, *Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products—Content and Format*, 8 (Oct. 2011) (Warning Guidance), http://bit.ly/2gTQC0q ("Only known hazards, and not theoretical possibilities can be the basis for contraindications.")

Setting aside Par's inconsistencies, DDIs like the interaction between divalproex and sodium oxybate increase the risk that patients will experience negative side effects. Indeed, FDA's resources for consumers state that

> Drug-drug interactions occur when two or more drugs react with each other. This drug-drug interaction may cause you to experience an unexpected side effect. For example, mixing a drug you take to help you sleep (a sedative) and a drug you take for allergies (an antihistamine) can slow your reactions and make driving a car or operating machinery dangerous.[12]

That concern is directly on point here. Sodium oxybate is a central nervous system (CNS) depressant with strong sedative properties. As discussed in Jazz's Petition, obtundation (*i.e.*, lowered levels of awareness or consciousness) was observed during clinical trials in patients receiving the recommended dose of Xyrem.[13] As a result, the labeling for Xyrem warns that patients "should not engage in hazardous occupations or activities requiring complete mental alertness or motor coordination, such as operating machinery or a motor vehicle or flying an airplane, for at least 6 hours."[14] The Medication Guide similarly identifies "changes in alertness" as a "serious side effect[]"[15] and instructs patients to not "drive a car, use heavy machinery, fly an airplane, or do anything that is dangerous or that requires you to be fully awake for at least 6 hours."[16]

Further, the sedative/depressant effects of sodium oxybate are dose-dependent.[17] This means that the risk of negative side effects—like disorientation, reduced attention or awareness, or increased confusion—increases with exposure to sodium oxybate.[18] A clinical study sponsored by Jazz in 2012 discovered that the anti-epileptic drug known as divalproex interacts with sodium oxybate when the two are administered concomitantly. The final results, which were received in April of 2013, showed that co-administration of divalproex was seen to increase systemic exposure to sodium oxybate by a mean of 25% and by more than 50% in some subjects (AUC range up to 1.7). And, this increase in exposure was associated with a significant increase in cognitive impairment and performance deficits, as measured by psychomotor testing. Importantly, the drug-drug interaction and the performance deficits identified were observed using a dose of Xyrem (6 grams) that is well within its recommended dosing range.[19]

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[12] FDA, *Drug Interactions: What You Should Know* (Mar. 2004), http://bit.ly/2gNKyIz.

[13] *See generally* Petition at 2-7.

[14] Xyrem Package Insert § 5.1.

[15] Xyrem Medication Guide at 1.

[16] *Id.*

[17] *See* Xyrem Package Insert §§ 5.6, 6.1, 9.2

[18] *See* Xyrem Medication Guide at 3 ("Your side effects may increase when you take higher doses of Xyrem.").

[19] *See generally* Petition, Exhibit 4.

In light of this discovery, Jazz filed a supplement in June 2013 to update the labeling for Xyrem, which was approved by FDA in April 2014. A warning regarding the concurrent use of Xyrem and "sedating anti-epileptic drugs" was added to the *Warnings and Precautions* section of Xyrem's package insert. Information identifying and explaining the divalproex DDI was added to the *Clinical Pharmacology* section. In addition, instructions to reduce the dose of Xyrem and monitor patients who are also taking divalproex were added to the *Highlights of Prescribing Information*, the *Dosage and Administration* section, and the *Drug Interactions* section. When FDA approved these changes, the agency chose to announce them in its monthly MedWatch alert regarding important "Safety Labeling Changes."[20]

Less than a year later, FDA approved the Xyrem REMS Program, to replace the risk management program (RMP) that had been in place for Xyrem since 2002. The goals of the REMS include mitigating "adverse outcomes resulting from inappropriate prescribing" and the objectives include both informing stakeholders about the "risk of significant CNS and respiratory depression" and screening "for concomitant use of sedative hypnotics and other potentially interacting agents."[21] The REMS therefore requires several specific actions to mitigate the risk that sodium oxybate will interact with other agents, including divalproex. They include, among other things, (1) obtaining the prescriber's verification that s/he has read and understands a Prescriber Brochure that reiterates the labeled dosing instructions regarding the divalproex DDI; (2) requiring prescribers to screen patients for concomitant medications and list all known medications on the Prescription Form; (3) requiring the pharmacist to counsel new patients and specifically ask whether they are also taking divalproex; (4) requiring the pharmacist to consult with the prescriber regarding concomitant use of divalproex prior to dispensing, unless prescriber knowledge of the concomitant use has already been confirmed; and (5) updating and reviewing records of all concomitant medications in a centralized database.[22]

FDA's approval of the Xyrem package insert in April 2014 and the Xyrem REMS Program in February 2015 demonstrates that the divalproex DDI is a safety concern, one that is unquestionably relevant to both the Xyrem patient population and their healthcare providers. The centralized database implemented as part of the Xyrem REMS Program indicates that more than 1 out of every 90 Xyrem patients who reported concomitant medications and/or comorbidities in the past year were also taking divalproex. Dr. Leslie Benet, a world-renowned pharmacologist, has explained that information regarding the divalproex DDI is important for prescribers, particularly those treating patients on a stable dose of Xyrem when divalproex is first administered, because such patients have developed expectations as to how they respond to Xyrem and may not be prepared to deal with an unexpected increase in sedation or other cognitive side effects.[23]

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[20] *See* FDA, *MedWatch Safety Alerts, April 2014 Safety Labeling Changes*, http://1.usa.gov/1TstVMw (last updated May 16, 2014).

[21] Xyrem REMS Document, §§ I, I.A.1, I.B.1.

[22] *See* Petition at 6-7.

[23] Petition, Exhibit 13 ¶¶ 19-20.

In sum, the divalproex DDI presents a real safety risk. As we show next, Par's various attempts to portray that risk as merely theoretical are without merit.

A. Information Related To The Divalproex DDI Was Added By A Timely Prior Approval Supplement Because That Is What The Law Required.

Par first asserts that the divalproex DDI does not present a safety concern because the relevant labeling changes were made through a Prior Approval Supplement (PAS) rather than a Changes Being Effected (CBE) supplement.[24] This argument fails for several reasons. First, the applicable regulation expressly requires a PAS for "any change to the information required by 201.57(a) of this chapter,"[25] *i.e.* the *Highlights of Prescribing Information* section of the labeling.[26] In fact, the regulation also forbids the use of a CBE supplement "for changes to the information required in 201.57(a) of this chapter" and reiterates that such changes must be made through a PAS "under paragraph (b)(2)(v)(C)."[27] Because the dosing instructions and other information regarding the divalproex DDI warranted inclusion in the *Highlights*, FDA's regulation forbade Jazz from filing a CBE and mandated the submission of a PAS.[28]

Second, the regulation also requires a PAS for all "major" changes to the approved labeling of a prescription drug.[29] According to FDA guidance, labeling changes "based on postmarketing study results," and changes "to the clinical pharmacology or the clinical study section reflecting new or modified data" are examples of major changes that "must be submitted in a prior approval supplement."[30] Those are precisely the types of information that Jazz was seeking to add to the Xyrem package insert regarding the divalproex DDI. Thus, contrary to what Par now asserts, Jazz did not "fail[] to submit a CBE supplement."[31] Rather, Jazz submitted a PAS because that was what FDA's regulations required and what FDA recommended in its guidance.

Third, Par attempts to mislead when it suggests that Jazz delayed submitting a PAS. Par tries to create the appearance of delay by contrasting the fact that the study was

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[24] Par Comment at 5.

[25] 21 C.F.R. § 314.70(b)(2)(v)(C).

[26] 21 C.F.R. § 201.57(a).

[27] 21 C.F.R. § 314.70(c)(6)(iii).

[28] Although guidance cannot change the plain meaning of a regulation, the relevant guidance for industry underscores that "[w]ith minor exceptions, changes to Highlights require a prior approval supplement." FDA, *Guidance for Industry: Labeling for Human Prescription Drug and Biological Products—Implementing the PLR Content and Format Requirements*, 22 (Feb. 2013) (PLR Guidance), http://bit.ly/2i0OgxA. It also indicates that this requirement can be waived only by FDA, not the sponsor. *See id.* ("The review division may permit changes to Highlights through a CBE supplement after consideration of the new information.").

[29] 21 C.F.R. § 314.70(b)(v).

[30] FDA, *Guidance for Industry: Changes to an Approved NDA or ANDA*, 24 (Apr. 2004) (Supplement Guidance), http://bit.ly/2hl5rXh.

[31] Par Comment at 5.

"conducted" in 2012 with the fact that the PAS was submitted in June 2013.[32] In truth, the final results from the study were not provided to Jazz by the researchers until April 2013. The PAS was submitted as soon as practicable, two months later.

Finally, Par's assertion that Jazz did not "claim a safety issue . . . at the time it filed the labeling amendment" is patently false.[33] The pre-specified objectives of Jazz's clinical study included an evaluation and comparison of the safety and tolerability of Xyrem with and without co-administration of divalproex tablets. Based on the final study results, Jazz proposed several changes to the labeling for Xyrem. One proposal was the insertion of new language regarding the concurrent use of "sedating anti-epileptic drugs" (*i.e.*, the class that includes divalproex) in the *Warnings and Precautions* section. That proposal was approved by FDA in April 2014. As a result, the current approved labeling for Xyrem now includes the following warning:

> The concurrent use of Xyrem with . . . sedating anti-epileptic drugs . . . may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death.[34]

As discussed in Jazz's Petition (and below), this general warning does not educate prescribers about the divalproex DDI, let alone the dosing changes and monitoring needed to safely and effectively co-administer Xyrem and divalproex. Nevertheless, the general warning in section 5.1 was indisputably updated in April 2014 to address the safety issues posed by concurrent use of sodium oxybate and divalproex.

B. Par's Classification Of Labeling Sections Is Nonsensical.

Par next argues that the divalproex DDI is not discussed in any sections of the Xyrem package insert that are "safety-related."[35] Par similarly claims that the sections of the labeling for Xyrem that do discuss the divalproex DDI are not "intended to convey information related to the safe use of the product."[36] According to Par, the only labeling sections that actually address safety concerns are the *Warnings and Precautions* and the *Contraindications* sections.[37] Par concludes that information "necessary to the safe use of [a drug]" must be "conveyed as a warning, precaution, or contraindication."[38]

This argument is frivolous. As just discussed, Jazz proposed in 2013, and FDA approved in 2014, a general warning regarding the risks posed by concurrent use of Xyrem and sedating anti-epileptic drugs, which Par completely failed to mention. Par likewise failed to acknowledge that the specific interaction between divalproex and sodium oxybate

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[32] *Id.*

[33] *Id.* at 7.

[34] Xyrem Package Insert § 5.1

[35] Par Comment at 2.

[36] *Id.* at 2, 6.

[37] *Id.* at 6.

[38] *Id.* at 7.

is discussed in the *Highlights of Prescribing Information* for Xyrem. Information contained in the *Highlights* section is defined to be "significant to the clinical use of the drug" and to have "significant clinical implications for practitioners."[39] Put another way, the *Highlights* section condenses "crucial prescribing information" to which "practitioners most commonly refer and regard as most important."[40] Par's discussion of Xyrem's labeling is just woefully incomplete.

Perhaps more importantly, neither the FDCA nor FDA's regulations categorizes sections of prescription drug labeling as "safety" and "non-safety" related. Rather, the safety (and risk-benefit ratio) of a prescription drug product is assessed according to the totality of its labeling.[41] As a result, all prescription drug labeling sections can and do convey important safety information. Thus, *Clinical Pharmacology* should include "pertinent negative findings that are informative for the safe and effective use of the drug," as well as "relevant PK measures and parameters that are important for the safe and effective use of the drug."[42] Similarly, *Dosage and Administration* should "contain[] all the information needed for safe and effective dosing and administration of a drug," including "safety monitoring procedures."[43]

In fact, Xyrem's labeling presents the divalproex DDI exactly as required by the Physician Labeling Rule (PLR) and recommended by FDA guidance. The *Drug Interactions* section should "contain a description of clinically significant interactions"[44] because this information is "generally . . . essential for prescribers to appropriately use the drug."[45] When an interaction "has important implications for the safe and effective use of the drug," relevant information "may be distributed among several other labeling sections (e.g., *Dosage and Administration*, *Contraindications*, *Warnings and Precautions*, or *Patient Counseling Information*), with a cross-reference to the *Drug Interactions* or *Clinical Pharmacology* sections for more detailed information."[46] Here, detailed information regarding the divalproex DDI is included in both the *Drug Interactions* section and the *Clinical Pharmacology* section of Xyrem's approved labeling, with additional information regarding the DDI in the *Dosage and Administration* section, cross-references in *Highlights*

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[39] 71 Fed. Reg. 3922, 3938 (Jan. 24, 2006).

[40] PLR Guidance at 5.

[41] *See* 21 U.S.C. § 355(d)(1) (safety of a new drug is assessed "under the conditions prescribed, recommended, or suggested in [its] proposed labeling"); *see also* 71 Fed. Reg. at 3934 ("Under the act and FDA regulations, the agency makes approval decisions based not on an abstract estimation of its safety and effectiveness, but rather on a comprehensive scientific evaluation of the product's risks and benefits under the conditions of use prescribed, recommended, or suggested in the labeling.").

[42] FDA, *Guidance for Industry: Clinical Pharmacology Section of Labeling for Human Prescription Drugs and Biological Products—Content and Format*, 3, 9 (Dec. 2016), http://bit.ly/2haqH62.

[43] FDA, *Guidance for Industry: Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products—Content and Format*, 1, 3 (Mar. 2010), http://bit.ly/2hAokHh.

[44] 21 C.F.R. § 201.57(c)(8)(i).

[45] FDA, *Draft Guidance for Industry: Drug Interaction Studies—Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*, 58 (Feb. 2012), http://bit.ly/2h5mugq.

[46] *Id.* at 61.

section, and a general warning regarding concurrent use of Xyrem and sedating anti-epileptic drugs in the *Warnings and Precautions* section.

Finally, Par has no response to FDA's characterization of the April 2014 labeling update. FDA identified the April 2014 update as a "Safety Labeling Change," warranting its inclusion in FDA's monthly update to MedWatch, which FDA describes as the "gateway for clinically important safety information."[47] Rather than address FDA's announcement, Par notes that FDA did not exercise its authority to mandate a labeling change,[48] which is a non-sequitur. Manufacturers can, do, and should add safety information to their products' labeling without prompting from FDA.[49] In this case, there was neither need nor opportunity for FDA to invoke section 505(o)(4) because Jazz alerted FDA to the divalproex DDI soon after it was discovered and, at the same time, proposed labeling changes to address it.

C. The Divalproex DDI Is Relevant To Clinical Practice.

Par also asserts that information regarding the divalproex DDI can be omitted from the labeling for generic sodium oxybate because the interaction does not exist "in . . . Clinical Practice."[50] The only support for this astonishing claim is Par's assertion that no adverse events related to divalproex have been reported for Xyrem.[51] Par thus assumes that manufacturers and FDA are limited to reacting to adverse events after they have already occurred. In truth, prescription drug regulations in general, and the PLR in particular, are intended to mitigate risks and, hopefully, prevent negative outcomes before they arise and patients are harmed.

In any event, Par's assertion that the divalproex DDI lacks a "connection to the actual Xyrem patient population" is factually incorrect.[52] Par has never sold a bottle of sodium oxybate and has no direct knowledge regarding Xyrem's patient population. In truth, many patients currently relying on Xyrem are concomitantly taking divalproex. Of Xyrem patients reporting concomitant medications and/or comorbidities in the past year, over 100 were taking divalproex.

As Dr. Benet explained, those patients and their prescribers benefit from REMS aspects and labeling instructions regarding the divalproex DDI. Dr. Benet explained that

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[47] FDA, *MedWatch: The FDA Safety Information and Adverse Event Reporting Program* (last visited on Jan. 11, 2017), http://www.fda.gov/Safety/MedWatch/.

[48] *See* Par Comment at 4.

[49] *See* 71 Fed. Reg. at 3934 ("Changes to labeling typically are initiated by the sponsor . . . ."); *see also Wyeth v. Levine*, 129 S. Ct. 1187, 1197-98 (2009) ("[T]hrough many amendments to the FDCA and to FDA regulations, it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times. It is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market.").

[50] Par Comment at 6

[51] *See id.* at 2, 4, 7-8.

[52] *Id.* at 8.

information regarding the divalproex DDI is important for prescribers, particularly because the interaction results in an increase in exposure to sodium oxybate, a drug with a steep dose response curve, narrow margin of safety, and which has been associated with significant adverse events even at recommended doses.[53] As Dr. Benet further explained, the divalproex DDI information is especially relevant for those already on a stable dose of Xyrem when divalproex is first administered, because such patients have developed expectations as to how they respond to Xyrem and may not be prepared to deal with an unexpected increase in residual sedation or other cognitive side effects.[54] It is notable that Par chose to ignore Dr. Benet's report.

II. Par's Labeling Proposals Violate 21 C.F.R. § 314.127(a)(7).

Par's precise labeling proposals are not public. Yet it is clear from its Comment that Par intends to both omit (*i.e.*, "carve out") the sections of Xyrem's labeling and the aspects of the Xyrem REMS Program excerpted in Appendices A and B to Jazz's Petition.[55] At the same time, Par apparently intends to add (*i.e.*, "carve in") new language to the labeling for its generic product to advise prescribers "not to administer [sodium oxybate and divalproex] together."[56] Neither proposal is permissible under the FDCA or 21 C.F.R. § 314.127(a)(7).

To prove that a proposed generic drug "will have the same clinical effect and safety profile" as the RLD,[57] an ANDA filer usually must prove that the labeling for the proposed generic will be "the same as" the labeling for the pioneer drug.[58] An ANDA filer can request FDA's permission to depart from the same labeling requirement and omit information regarding a "use" that is covered by a patent or exclusivity,[59] but the regulation prohibits omissions that render the generic drug "less safe or effective than the [RLD] for all remaining, nonprotected conditions of use."[60] FDA has stressed that the carve-out "exception[] to the requirement of 'same labeling' [is] limited."[61] A labeling carve out must not result in "diminished safety or effectiveness" because "the purpose of section 505(j) of the act . . . is to assure the marketing of generic drugs that are as safe and effective as their brand-name counterparts."[62]

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[53] Petition, Exhibit 13 ¶ 19.

[54] *Id.* ¶ 20.

[55] *See, e.g.*, Par Comment at 9 ("Par's proposed labeling that omits the protected condition of use").

[56] *Id.* at 8.

[57] *Sanofi-Aventis U.S. LLC v. FDA*, 733 F. Supp. 2d 162, 164 (D.D.C. 2010).

[58] 21 U.S.C. §§ 355(j)(2)(A)(v), 355(j)(4)(G); *see also, e.g.*, *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 614 (2011) ("generic drug manufacturers have an ongoing federal duty of 'sameness'").

[59] *See* 21 C.F.R. §§ 314.94(a)(8)(iv), 314.94(a)(12)(iii)(A).

[60] 21 C.F.R. § 314.127(a)(7).

[61] 54 Fed. Reg. 28872, 28879 (July 10, 1989).

[62] *Id.* (emphasis added).

Importantly, the burden is on Par to demonstrate that its generic product will not be rendered less safe or effective by its proposed labeling and REMS omissions. Par bears that burden both as the ANDA filer seeking FDA's approval,[63] and as the party trying to invoke an exception to the statutory "same labeling" requirement.[64] This burden can only be satisfied with reliable evidence,[65] not speculation or conclusory statements.[66] But that is all Par has to offer. The fact is, concomitant use of divalproex and sodium oxybate can and does occur in clinical practice. Co-administering those two drugs results in an interaction that can increase patient exposure to sodium oxybate, in some cases by more than fifty percent. Increased exposure to sodium oxybate in turn increases the risk of sedation and sedation-related risks identified in Xyrem's labeling, including the risks of cognitive and performance deficit. The approved labeling and REMS for Xyrem address these risks by, among other things, (a) identifying the divalproex DDI; (b) screening for, and keeping records regarding, the concomitant use of sodium oxybate and divalproex; (c) providing dose-adjustment instructions permitting the safe co-administration of both agents; and (d) instructing providers to carefully monitor patients when the two drugs are co-administered.

If Par's proposal is accepted none of this will occur for Par's product. Prescribers will not be informed about the potential divalproex DDI, no screening for co-administration will occur, prescribers will not be alerted when co-administration is identified, no instructions for safe co-administration will be provided, and patients taking both drugs will not be monitored. There is simply no basis for Par's claim that it is "confident" that its proposal will not result in diminished safety or efficacy.[67]

A. Par Cannot Define Away The Risks Posed By Concomitant Use Of Sodium Oxybate And Divalproex Sodium.

Par attempts to sidestep the divalproex DDI altogether by defining the unprotected use for purposes of 21 C.F.R. § 314.127(a)(7) as the use of "sodium oxybate without concomitant use of divalproex."[68] This is an impermissible sleight of hand. Par cannot carve out a method of mitigating the risks posed by a DDI simply by defining the remaining,

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[63] *See* 5 U.S.C. § 556(d) ("the proponent of a rule or order has the burden of proof"); 21 C.F.R. § 12.87(d) ("the [party] who is contending that the product is safe or effective or both and who is requesting approval . . . has the burden of proof in establishing safety or effectiveness or both and thus the right to approval").

[64] *See, e.g.*, *United States v. Regenerative Sciences, LLC*, 741 F. 3d 1314, 1322 (D.C. Cir. 2014) (party invoking "an exception from the otherwise applicable provisions of the FDCA . . . bear[s] the burden of establishing that it applies") (citing *United States v. First City Nat'l Bank of Houston*, 386 U.S. 361, 366 (1967); *FTC v. Morton Salt Co.*, 334 U.S. 37, 44-45 (1948)).

[65] *See, e.g.*, 5 U.S.C. § 556(d) (requiring "reliable, probative, and substantial evidence"); 21 C.F.R. §§ 12.24(b)(2), 12.94(c)(1)(i), 12.94(d)(1)(i), 12.120(b)(1), 12.130(c) (each requiring reliable evidence); *see also U.S. Steel Mining Co. v. Office of Workers' Comp. Progs.*, 187 F.3d 384, 388-389 (4th Cir. 1999) ("Absent such a discipline to qualify evidence, administrative findings and orders could unacceptably rest on suspicions, surmise, and speculation.").

[66] *See, e.g.*, *Amerijet Int'l, Inc. v. Pistole*, 753 F.3d 1343, 1350-51 (D.C. Cir. 2014).

[67] Par Comment at 9.

[68] *Id.* at 10 (emphasis removed).

unprotected use to exclude the interaction. If this were a valid construction of the regulation, the limited exception codified in 21 C.F.R. 314.127(a)(7) would swallow the same labeling rule. Literally any interaction could be sidestepped in the same manner—the ANDA filer could simply exclude co-administration of the relevant agent from the labeling of the proposed generic.[69]

The problem with Par's approach is that the proposed omitted use—concomitant use with divalproex—will remain relevant to any and all patients who take sodium oxybate (whether Xyrem or a generic product). Sodium oxybate is approved to treat certain symptoms of narcolepsy. At any point in time, narcolepsy patients taking sodium oxybate may also experience a condition that can be treated with divalproex, such as migraines, seizures, or mania.[70] Should that occur, those patients and their prescribers will need the dosing instructions and other information in Xyrem's labeling to enable the safe co-administration of the two agents. There is nothing speculative about that need—experience under the Xyrem REMS Program shows that concomitant use of the two drugs occurs in clinical practice.

Par therefore errs when it tries to rely on FDA's decisions regarding Camptosar (irinotecan hydrochloride) and Prandin (repaglinide).[71] In both those examples, the products were approved for an unprotected monotherapy and a protected combination therapy.[72] In that situation, the protected and unprotected uses define distinct patient populations. The ability to identify distinct patient populations allowed FDA to reasonably conclude that omitting information about the protected use would not adversely affect the safety or efficacy of the generic drug for the remaining, unprotected use.[73] Here, however, Xyrem and divalproex are not approved as a "combination" therapy for any condition, and there is no "monotherapy" that Par can cite as an unprotected use under 21 C.F.R. § 314.127(a)(7). Rather, the patent-protected labeling information and REMS measures regarding the divalproex DDI apply equally to both of Xyrem's approved indications.

Par similarly misunderstands FDA's prior decisions regarding Colcrys (colchicine) and Rapamune (sirolimus). FDA did not allow dosing instructions regarding a protected use involving Colcrys (acute treatment) to be carved out because the protected use could

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[69] Indeed, the Office of New Drugs routinely rejects similar efforts to define away risks. If Par's approach were permissible, NDA holders could unilaterally narrow the conditions of use for their product to exclude concomitant uses, thereby avoiding the need to include warnings in the labeling for their products (or risk mitigation measures in the REMS for their products) regarding the interaction.

[70] Divalproex is FDA-approved to treat manic episodes, as monotherapy or adjunctive therapy for seizures, and as prophylaxis of migraine headaches. *See generally* Depakote Package Insert, NDA 018723.

[71] *See* Par Comment at 9-10.

[72] *See* Citizen Petition Response, FDA Docket No. FDA-2008-P-0069 (July 28, 2008) (Camptosar Response); Citizen Petition Response, FDA Docket Nos. FDA-2008-P-0343 and FDA-2008-P-0411 (Dec. 4, 2008) (Prandin Response).

[73] *See, e.g.*, Camptosar Response at 10 ("this omitted information relates to use of irinotecan as combination therapy and is not necessary for the safety or effectiveness of irinotecan as monotherapy").

become relevant to any patient at any time.[74] FDA also refused to allow dosing instructions regarding a DDI involving Colcrys to be omitted because any patient might require treatment with the interacting agents.[75] Likewise, in the Rapamune case, FDA found that information regarding the protected use (a cyclosporine-sparing regimen) could not be omitted because it might become relevant even in the "narrow subset of renal transplant patients at high risk for rejection" proposed by ANDA filers.[76]

Par cannot distinguish those decisions in any meaningful way. It notes that FDA requested or required the studies in those cases, while Jazz voluntarily initiated its study.[77] In addition, Par contrasts the length of time that Xyrem was marketed without the protected use with the shorter periods for Rapamune and Colcrys.[78] These differences are irrelevant under 21 C.F.R. § 314.127(a)(7), which asks simply whether the proposed omission will render the generic product less safe or effective than the RLD for the remaining unprotected use. As the Colcrys example particularly teaches, removing dosing instructions and other labeling information regarding a potential DDI will result in a less safe and effective product.[79]

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[74] *See* Colcrys Response at 24 ("To the extent that a healthcare provider determines it is necessary to use colchicine for treatment of an acute gout flare in a patient receiving colchicine for prophylaxis, adequate information about potential toxicity of colchicine dosing would be important to minimize the risk of cumulative toxicity.").

[75] *See id.* at 19-20 ("FDA agrees that product labeling for any single-ingredient oral colchicine product needs to include adequate information on drug-drug interactions, including relevant dose adjustments needed to prevent unnecessary toxicity.").

[76] Citizen Petition Response, Docket No. FDA-2003-P-0518, 4 (Sept. 20, 2004) ("Information on the potential hazard of prolonged use of cyclosporine with sirolimus and the potential benefit of a cyclosporine-sparing regimen is needed to use the drug safely and effectively, even in the limited high-risk population. In particular, patients who were classified as high-risk because of their baseline characteristics, but who remain free of rejection episodes for 6 to 12 months post transplantation, may in fact be reclassified as low to moderate risk and conceivably could benefit from a cyclosporine-sparing regimen.").

[77] Par Comment at 11-12

[78] *Id.*

[79] Par's discussion of the Skelaxin (metaxalone) precedent is similarly misguided. Although FDA did say in March 2004 that certain pharmacokinetic information regarding the relative bioavailability of Skelaxin when taken food could be omitted from the labeling for generic metaxalone. In doing so, FDA emphasized that—unlike here—the information in question had not resulted in any changes to the *Dosage and Administration* section of Skelaxin's package insert. *See* Letter from Gary J. Buehler re: ANDA for Metaxalone Tablets, 3-4 (Mar. 1, 2004). According to FDA, such an omission would not render the generic product less safe or effective because "the clinical effect of the increased bioavailability is unknown." *Id.* at 4. In contrast, the increased sodium oxybate exposure caused by the divalproex DDI is associated with a significant increase in cognitive impairment. Par is also wrong to assert that FDA "actually permitted the particular carve-out in question" in Skelaxin. Par Comment at 13. In fact, FDA never approved an ANDA for generic metaxalone with a labeling carve out because the issue was mooted by patent litigation. Moreover, there is reason to believe that FDA subsequently reconsidered its position regarding the carve out. In November 2004, a metaxalone ANDA filer amended its application to include paragraph IV certifications to the patents covering the use that FDA had earlier indicated could be carved out. Such an action—which caused the ANDA to remain unapprovable for at least 30 more months—would have made no sense if FDA continued to believe that a labeling carve out was permissible. *See* Memorandum from Martin Shimer, Branch Chief, Regulatory Support

Par also notes that the relevant DDI for Colcrys had caused fatalities and was, therefore, well known within "the medical community."[80] But 21 C.F.R. § 314.127(a)(7) surely does not require proof of fatalities—an increased risk of adverse side effects through an undisclosed DDI is clearly enough to render a proposed generic drug less safe and effective than the RLD. Moreover, the fact that Xyrem's label is the only source of the divalproex DDI information[81] just underscores how ill-advised Par's proposed omissions truly are. A prescriber confronted with generic labeling that omitted the protected divalproex DDI information would have to somehow divine that divalproex interacts with sodium oxybate and then guess how to proceed.[82]

B. Par Cannot Add New Warnings Or Contraindications.

Because the divalproex DDI information is relevant to both of Xyrem's approved indications, its omission necessarily results in a less safe and less effective product. If the divalproex DDI information is carved out, then prescribers will have only the information in the general warning in section 5.1 of the Xyrem package insert. To be sure, section 5.1 was updated in 2014 with a general warning regarding the concurrent use of Xyrem and sedating anti-epileptic drugs. But, as explained in Jazz's Petition, a general warning about concurrent use does not address or educate prescribers regarding the potential for interacting effects. Thus, prescribers relying on section 5.1 when co-administering divalproex with sodium oxybate might understand that the overall level of sedation experienced by the patient would be higher because both drugs cause sedation. But prescribers would not understand that, in addition to the additive sedative effect, patients administered divalproex and sodium oxybate in combination may also experience a greater than 50% increase in sodium oxybate exposure due to the interaction between the two drugs. Those prescribers also would not be aware of the specific dosing adjustments required to safely and effectively account for the potential drug-drug interaction.[83]

Par does not deny that its carve out would result in the above deficiencies. Instead, Par proposes to add new labeling language instructing prescribers to not co-administer generic sodium oxybate and divalproex at all.[84] This proposed "carve in" (an instruction "not to" administer the two drugs concomitantly) is indistinguishable from a

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Branch, Office of Generic Drugs to ANDA 040445 re: Background for Sandoz' Metaxalone Tablets, 800mg; Decision regarding non-forfeiture of 180-day exclusivity, 5-6 (Mar. 29, 2010).

[80] Par Comment at 12.

[81] As previously mentioned, the PTAB ruled that medical literature prior to Jazz's discovery did not disclose the divalproex DDI or the method of safely administering divalproex and sodium oxybate. *See* Petition at 3-4.

[82] *See id.* at 11-12.

[83] *See id.*

[84] *See, e.g.*, Par Comment at 8 ("physicians would be advised not to administer the two drugs together") (emphasis in the original); *id.* at 11 ("additional minor labeling changes to make clear that concomitant use of divalproex sodium is not approved").

contraindication.[85] Allowing Par to add a new contraindication to the labeling for sodium oxybate would be plainly unlawful.

First, there are clear regulatory standards that must be met before a contraindication is appropriate in prescription drug labeling. Contraindications are reserved for situations where "the risk of use (e.g., certain potentially fatal adverse reactions) clearly outweighs any possible therapeutic benefit."[86] While the divalproex DDI clearly presents a risk of use (*i.e.*, an increase in systemic exposure to sodium oxybate and the attendant increased risk of negative side effects), that risk is manageable through dosing adjustments and, therefore, does not warrant a contraindication. Moreover, allowing Par to include an unwarranted contraindication would be contrary to the public health[87] and would result in decreased efficacy. As proposed by Par, the labeling for generic sodium oxybate product would explicitly "discourage[e] appropriate use of a beneficial drug,"[88] when a patient presents a need for treatment with both sodium oxybate and divalproex. That decrease in efficacy would itself violate 21 C.F.R. § 314.127(a)(7), a point Par completely ignores in its Comment.

Second, Par's proposed "carve in" violates the same labeling requirement in section 505(j) of the FDCA.[89] The agency has stated that the exceptions to the same labeling rule do not allow ANDA filers to include "additional warnings or precautions" in the labeling for a generic product,[90] or "better directions regarding how the drug should be taken."[91] Indeed, FDA has specifically stated that the labeling for a proposed generic product cannot include new "contraindications" or "other safety information" not present in the RLD's labeling.[92]

Par's contention that FDA has previously allowed ANDA filers to draft and include new instructions in the labeling for their generic products is misleading.[93] The Lyrica (pregabalin) and Treanda (bendamustine hydrochloride) citizen petition responses merely allowed the ANDA filers to remove references to the protected use.[94] The Oxandrin

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[85] *See* Warning Guidance at 7 (identifying labeling terminology such as "Drug X should not be used" and "Do not use" as "a contraindication").

[86] 21 C.F.R. § 201.57(b)(5).

[87] *See, e.g.*, 71 Fed. Reg. at 3935 ("Overwarning, just like underwarning, can similarly have a negative effect on patient safety and public health."); *id.* at 3927 ("FDA believes that including relative or hypothetical hazards diminishes the usefulness of the [contraindications] section").

[88] 73 Fed. Reg. 2848, 2851 (Jan. 16, 2008).

[89] 21 U.S.C. §§ 355(j)(2)(A)(v), 355(j)(4).

[90] 57 Fed. Reg. 17950, 17593 (Apr. 28, 1992).

[91] *Id.* at 17957.

[92] *Id.* at 17961.

[93] Par Comment at 11 & n.38.

[94] As to Lyrica, FDA allowed revisions "to prevent disclosure of aspects of the RLD labeling protected by patents or exclusivity." Citizen Petition Response, Docket No. FDA-2010-P-0087, 9 (July 30, 2010) (Lyrica Response). For example, FDA allowed a warning to be revised to avoid using the term "epilepsy" or "anti-epileptic," in recognition of the patent-protected epilepsy indication. *Id.* at 9-10. As to Treanda, FDA allowed

(oxandrolone) response allowed the inclusion of language required under a separate regulation and did not allow the ANDA filers to include any new information regarding clinical use of the drug.[95] To the best of Jazz's knowledge, FDA has never allowed an ANDA filer to create and include new clinical instructions not found in the labeling for the RLD, as Par proposes to do here.

Third, even if the same labeling requirement could be twisted to allow a labeling "carve in," adding a new instruction regarding divalproex would violate the separate statutory requirement that the labeled "conditions of use" for a generic drug have been previously approved for the RLD.[96] In this context, the phrase "conditions of use" refers to much more than just the indications that have been approved for the RLD. Rather, it refers comprehensively "to how, to whom, and for which purposes a drug product is used by physicians and patients."[97] Adding new labeling language instructing against prescribing sodium oxybate to patients who are concomitantly prescribed divalproex would create a new condition of use that has never been approved for the RLD.

Fourth, Par's REMS changes would render its generic product less safe and effective even if it were allowed to "carve in" a contraindication regarding divalproex in the package insert for generic sodium oxybate. REMS requirements contribute to the risk-benefit profile of a drug,[98] and Par concedes that its omissions would affect the REMS for generic sodium oxybate.[99] The Xyrem REMS Program requires pharmacists to screen for, alert prescribers to, and review each patient's central database file for, concomitant divalproex usage.[100] These requirements are effectuated by specific references to divalproex sodium in the Xyrem REMS labeling, which increase the likelihood that a Xyrem prescriber is made aware of the concomitant use.

Even if Par is allowed to "carve-in" a contraindication or similar statement regarding divalproex, prescribers of generic sodium oxybate will still need to know whether their patients are also taking divalproex in order to comply with Par's instruction not to concomitantly administer the two drugs. Par, however, would remove all specific references to divalproex in its REMS labeling, and would not require pharmacists and

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"*de minimis* modifications in the labeling to remove references to the . . . protected indication." Citizen Petition Response, Docket No. FDA-2015-P-3980, 15 (Mar. 24, 2015) (Treanda Response).

[95] Citizen Petition Response, Docket No. 2005P-0383, 21 (Dec. 1, 2006) (Oxandrin Response) (allowing ANDA filers to include a statement that "Certain geriatric use information is protected by marketing exclusivity" in order to provide "accurate and appropriate" instructions per 21 C.F.R. § 201.80(f)(10)(vi)). The propofol situation, which Par did not cite, is similarly distinguishable. In that case, the ANDA product contained an inactive ingredient not present in the RLD, which triggered the inclusion of a sulfite warning under a pre-existing FDA regulation, 21 C.F.R. § 201.22(b). *See Zeneca, Inc. v. Shalala*, 213 F.3d 161, 169 (4th Cir. 2000).

[96] 21 U.S.C. §§ 355(j)(2)(A)(i), 355(j)(4)(B).

[97] Federal Defs. Mem. in Opp. to Pl.'s Mot. for Temporary Restraining Order and/or Preliminary Injunction, 20 (Apr. 17, 2012), Docket No. 22 in *Viropharma Inc. v. Hamburg*, No. 12-00584 (D.D.C.).

[98] *See generally* 21 U.S.C. § 355-1.

[99] Par Comment at 14, 16

[100] *See* Petition at 6-7.

prescribers to screen for divalproex use. Par also would not instruct prescribers on the appropriate dosing modifications to ensure safe use. Par's omissions would cause prescribers and pharmacists to be less likely to identify or be aware of concomitant use of sodium oxybate and divalproex and thus increase the risk that a patient receiving Par's product would be prescribed divalproex without the necessary dose adjustments and monitoring.[101]

Fifth, longstanding FDA policy holds that an ANDA filer who seeks to carve out a protected use may not include any language in the labeling for the generic that would disclose the protected use.[102] Where the protected use corresponds to an indication, FDA typically requires omission of the indication statement, dosing, and clinical studies information regarding the protected indication.[103] Even where applicable information is not carved-out (e.g., a warning that covers both the protected and unprotected uses), FDA generally removes all references to the protected use, to ensure that the ANDA labeling does not disclose that use.[104] Allowing Par to include a new contraindication regarding the divalproex DDI would violate that policy by revealing the protected use.

Finally, Par's proposed "carve in" would lead to confusion among patients, prescribers, and pharmacists. FDA has acknowledged that one of the important public policies animating the same labeling rule is the need to "avoid differences that might confuse health care professionals who prescribe and dispense prescription drug products."[105] Par has proposed a world in which the labeling for generic sodium oxybate and Xyrem's labeling would be diametrically opposed—the generic labeling would contraindicate the concomitant use of sodium oxybate and divalproex, while Xyrem's labeling would enable concomitant use through an evidence-based dose reduction and appropriate patient monitoring.

Contrary to Par's claim, there is a significant difference between "the numerous prior instances" where FDA has approved omissions of protected labeling information, and creating new labeling to advise physicians "not to administer the two drugs together."[106] It is one thing for generic labeling to remain silent about a protected use. It is something else entirely for generic labeling to affirmatively contradict the labeling for the RLD, which is what Par proposes. To reiterate, FDA has never before tolerated such a contradiction.

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[101] *See, e.g.*, Petition, Exhibit 13 ¶¶ 29-32.

[102] *See, e.g.*, Lyrica Response at 9; Treanda Response at 14-15.

[103] *See, e.g.*, Treanda Response at 11 n.43.

[104] *See, e.g.*, Treanda Response at 14, 16.

[105] 54 Fed. Reg. at 28881.

[106] Par Comments at 8.

C. Par Cannot Rely On Xyrem's Pre-2014 Labeling Or The Pre-2015 Risk Management Program To Justify Its Proposals.

Par repeatedly asserts that its proposed labeling omissions are justified because Xyrem was marketed from 2002 to 2014 without divalproex-specific labeling,[107] and because the risk management program in place until 2015 did not refer to divalproex.[108] The unspoken premise of Par's argument is that the risk-benefit ratio for generic sodium oxybate must be positive without information or REMS aspects related to the divalproex DDI because the risk-benefit ratio for Xyrem was deemed positive without such information or elements. But the comparison to a time when the divalproex DDI was not yet known is plainly not permissible under 21 C.F.R. § 314.127(a)(7).[109] Rather, an ANDA filer must demonstrate that its proposed generic product will be no less safe and effective for the unprotected use than the RLD, as the RLD is labeled today.

Allowing prior versions of labeling (or prior versions of risk management measures) to justify a labeling carve out also would be bad policy. Labeling and risk management measures necessarily evolve over time as new information and evidence is developed, either through clinical experience or investment in postmarket studies.[110] Here, Jazz discovered a potential DDI, invested in the studies necessary to establish its existence as well as a safe and effective way to address it through dosing adjustments. If that newly discovered information can be carved out simply because it post-dated FDA's original approval, then the incentives to engage in postmarket research will be severely undermined, if not destroyed altogether.[111]

III. Par's REMS Proposals Violate 21 U.S.C. § 355-1(i)(1)(B).

In addition to being impermissible from a labeling perspective, Par's proposal would also violate the REMS statute. Par claims that "nothing in the REMS statute indicates that it was meant to abrogate the section viii carve-out framework."[112] Par misunderstands how the law works. Section 505-1 of the FDCA, added in 2007, imposed new requirements for

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[107] *See id.* at 2, 3, 4, 10

[108] *See id.* at 14-15.

[109] For instance, in 2002, FDA refused to allow an ANDA applicant to "rely on information that has been discontinued" from the RLD's labeling. Citizen Petition Response, Docket Nos. 01P-0495, 02P-0191, & 92P-0252, 2 (June 11, 2002). FDA recently reiterated that it "must start with the currently approved labeling" when "considering whether a proposed ANDA can be approved" under 21 C.F.R. § 314.127(a)(7). Citizen Petition Response, Docket No. FDA-2016-P-2654, 9 (Nov. 28, 2016).

[110] *See, e.g.*, 71 Fed. Reg. at 3934 ("FDA continuously works to evaluate the latest available scientific information to monitor the safety of products and to incorporate information into the product's labeling when appropriate.").

[111] *Cf. CollaGenex Pharms., Inc. v. Thompson*, No. 03-1405, 2003 U.S. Dist. LEXIS 12523, at *35 (D.D.C. July 22, 2003) ("[T]here would be very little reason for a research company to invest millions of dollars only to have another company re-formulate the same drug, submit an ANDA, avoid the costs of development, charge less for its product, and assume dominance in the market."); *Fisons Corp. v. Shalala*, 860 F. Supp. 859, 862 (D.D.C. 1994) ("Congress intended the Hatch-Waxman Act to benefit pioneer drug manufacturers.").

[112] Par Comment at 16.

both pioneer and generic drugs. In enacting those requirements, Congress was supplementing, not abrogating, the approval standards that had been imposed in 1938, 1962, 1984, etc. As a result, an ANDA can be approved only if it complies with both the Hatch-Waxman requirements in section 505(j) and the generic REMS requirements in section 505-1(i).

Under the REMS statute, a generic drug must always be subject to the same elements to assure safe use (ETASU) as the RLD.[113] By default, the generic and the RLD are supposed to implement their respective ETASU through a single, shared system.[114] In certain situations specified in the statute, however, the single, shared system requirement (SSSR) can be waived by FDA.[115] Par's proposal—to not discuss and to require no risk mitigation actions regarding the divalproex DDI—would necessarily require a separate generic REMS and thus, a waiver of the SSSR. Agency officials have characterized waiving the SSSR as an option of "last resort,"[116] and Jazz does not believe the statutory requirements for a waiver have been met regarding sodium oxybate.

But, assuming for the sake of argument that a waiver could be possible, the statute still requires that the generic REMS include "comparable aspect[s] of the elements to assure safe use" in place for the RLD.[117] Jazz explained in the Petition that taking no action regarding the divalproex DDI (as Par proposes) is not "comparable" to the relevant aspects of the ETASU in place for Xyrem.[118]

In response, Par argues that the measures in the Xyrem REMS Program related to the divalproex DDI are not ETASU.[119] But Jazz never said they were. For present purposes, the relevant ETASU in the Xyrem REMS Program are the requirements that healthcare providers and the central pharmacy be specially certified.[120] As Par concedes, certification requirements for providers and pharmacists are among the ETASU that Congress explicitly endorsed when it enacted the REMS statute in 2007.[121]

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[113] 21 U.S.C. § 355-1(i)(1)(B).

[114] *Id.*

[115] *Id.* § 355-1(i)(1)(B)(i)-(ii).

[116] Elaine Lippmann, ORP, CDER, FDA, *Development of Single, Shared System REMS*, 12 (Oct. 26, 2016), http://bit.ly/2hEgvjU (hereinafter, "Lippmann Presentation").

[117] 21 U.S.C. § 355-1(i)(1)(B).

[118] *See* Petition at 13-14.

[119] *See, e.g.*, Par Comment at 16 ("Language in REMS Supporting Documents Regarding Concomitant Use of Divalproex Sodium Is Not an ETASU").

[120] Xyrem REMS Document at § II(B)(1), (2).

[121] *See* Par Comment at 17 & n.69 (citing 21 U.S.C. § 355-1(f)(3)). Contrary to what Par contends, the list of ETASU in section 505-1(f)(3) is not exhaustive. Through the transitional provisions of the Food and Drug Administration Amendments Act (FDAAA), Congress also endorsed all elements to assure safe use that had previously been implemented either as risk management programs under the Subpart H regulations or through agreement with FDA. *See* Pub. L. No. 110-85, § 909(b), 121 Stat. 823, 950-51 (Sept. 27, 2007).

Par also argues that REMS measures related to the divalproex DDI do not "constitute an aspect of any ETASU that must be 'comparable' under the statute."[122] Par asserts that "'aspects' contemplated under the statute embody the overall documents themselves."[123] Par offers neither explanation nor citation to support the notion that the statutory phrase "aspect of the elements to assure safe use" is limited to the "overall documents" appended to a REMS. Par's reading is clearly wrong. The word "aspect" generally means a "particular part or feature" of some larger whole.[124] Thus, an "aspect of the elements to assure safe use" broadly includes any constituent or subsidiary part or feature used to implement the ETASU required for the REMS. Notably, FDA officials agree that this is how to understand section 505(i)—they have indicated that "aspects" of ETASU broadly include any and all methods to "operationalize[]" the ETASU and that ANDA filers seeking to implement a separate generic REMS through a waiver of the SSSR must "explain and justify <u>any differences in operations</u>."[125]

Par compounds its error by misunderstanding the phrase "different, comparable." Par is correct to note that this does not mean "'identical.'"[126] But Par clearly errs when it argues that the phrase "different, comparable" opens the door for Par to freely alter, in its unilateral discretion, "any <u>non-essential</u> language" in the approved REMS documents for Xyrem so long as such changes have "<u>no material effect</u> on the actual ETASUs or administration of the program."[127] None of this has any basis in the law. The statute does not refer to "materiality" or "essentiality," and the comparability standard is a well established concept in federal drug regulation. To be comparable within the meaning of section 505-1, any differences in the aspects of an ETASU must not result in any adverse effect on safety or efficacy.[128]

Judged against the actual statutory standards, Par's proposal is clearly deficient. The prescriber and pharmacist requirements related to the divalproex DDI are all "aspects" of the certification ETASU in the Xyrem REMS Program. Those measures advance stated goals and objectives of the REMS,[129] and removing them "would reduce the likelihood that a Xyrem prescriber would be aware of (i) the interaction with divalproex; (ii) the instructed dose adjustment in the presence of divalproex; and (iii) the fact that a given

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[122] Par Comment at 16.

[123] *Id.* at 17.

[124] New Oxford American Dictionary (3d ed. 2010).

[125] Lippmann Presentation at 17 (emphasis added).

[126] Par Comment at 16.

[127] *Id.* at 17 (emphasis in the original).

[128] *Cf.* FDA, *Guidance for Industry: Q5E Comparability of Biotechnological/Biological Products Subject to Changes In Their Manufacturing Process*, 3 (June 2005) http://1.usa.gov/1EzkEid (comparability means that "any differences in quality attributes have no adverse impact upon safety or efficacy of the drug product"); Supplement Guidance at 6-7 ("equivalence" requires no adverse effect on quality characteristics).

[129] Par disingenuously suggests that the reference to "interacting agents" in the goals and objectives of the Xyrem REMS Program does not include divalproex. *See* Par Comment at 18. Given that the divalproex DDI is <u>actually addressed</u> in the REMS program documents, there is no legitimate basis for Par to try to read such a limitation into the goals or objectives of the REMS.

patient was concomitantly taking divalproex."[130] Removing them also "could potentially increase the risk to patients of a preventable adverse event or a loss of efficacy."[131] Because Par cannot discharge its burden of demonstrating comparability under section 505-1(i), its ANDA is not approvable as a matter of law, even if the SSSR could be waived and there was no labeling deficiency under 21 C.F.R. § 314.127(a)(7).

IV. Conclusion

For the foregoing reasons, and those discussed in Jazz's citizen petition, FDA should (1) refuse to approve any sodium oxybate ANDA that does not include in its proposed labeling the portions of the Xyrem package insert related to divalproex, and (2) refuse to approve any sodium oxybate ANDA that does not include the aspects of the Xyrem REMS Program related to divalproex.

V. Verification

Pursuant to 21 C.F.R. § 10.31(d), I certify that, to my best knowledge and belief: (a) I have not intentionally delayed submission of this document or its contents; and (b) the information upon which I have based the action requested herein first became known to me on or about November 17, 2016 (when Par's comments in opposition to Jazz's citizen petition were posted to www.regulations.gov). If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Jazz Pharmaceuticals, Inc. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this document.

Sincerely,

Philip J. Honerkamp
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(650) 496-3777

on behalf of Jazz Pharmaceuticals, Inc.

[130] Petition, Exhibit 13 ¶ 32

[131] *Id.*