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November 15, 2016

VIA ELECTRONIC DELIVERY

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

Re: Comments to Docket No. FDA-2016-P-2672

Dear Sir or Madam:

On behalf of our client, Par Pharmaceutical, Inc. ("Par"), we submit these comments to the above-referenced docket for a citizen petition (the "Citizen Petition") filed by Jazz Pharmaceuticals, Inc. ("Jazz"), manufacturer of the reference listed drug Xyrem® (sodium oxybate) (the "RLD") under new drug application ("NDA") No. 21-196. The Citizen Petition requests that the Food and Drug Administration ("FDA" or "the Agency") refrain from approving any abbreviated new drug application ("ANDA") referencing the RLD that does not include within its proposed labeling (including the associated risk evaluation and mitigation strategy ("REMS")) certain patent-protected information relating to co-administration of the proposed generic product with divalproex sodium. Jazz claims that omission of this patent-protected information would render such a proposed generic product less safe or effective than the RLD.

As discussed in these comments, the facts and circumstances giving rise to the Citizen Petition, the Agency's administrative precedent, and the legislative policy underlying the generic approval regime all dictate that the Citizen Petition must be denied by FDA:

- The Citizen Petition is the result of a patent-driven effort to prevent consumer access to lower cost generic drugs. In fact, the Citizen Petition is just the latest manifestation of Jazz's longstanding effort to protect its monopoly over sales of sodium oxybate drug products. FDA need not reach this conclusion on the basis of conjecture; rather, Jazz's own public statements confirm the anti-competitive intent of the Citizen Petition.

- Jazz cites safety issues in an effort to conceal its true anti-competitive motive. However, Jazz's claim that inclusion of the relevant labeling information is necessary to ensure the safe use of a generic sodium oxybate product is undermined by the chronology of Jazz's

own handling of the issue, the applicable regulations, and the Agency's administrative precedent:

- Jazz marketed the RLD for twelve (12) years before amending its label to include statements related to the interaction of sodium oxybate with divalproex sodium, and Jazz only took this step after it had first sought patent protection for these labeling statements. Indeed, Jazz submitted its method of use patent applications three (3) months before submitting a labeling amendment to its NDA, underscoring the patent-driven, not patient-driven, intent of its strategy.

- The applicable references to divalproex sodium do not appear in any portion of the RLD's labeling intended to communicate safety information to physicians or patients, such as the *Warnings and Precautions*, *Contraindications*, or *Adverse Reactions* sections. Apparently, at the time Jazz sought to amend its labeling, it did not believe the interaction of sodium oxybate with divalproex sodium created an issue sufficient to include it in the safety-related portions of the labeling. It is only now, when faced with competition, that Jazz cites a safety issue in the hopes of extending its monopoly for an additional nine (9) years.

- The lack of such references in the safety-related sections of the labeling should come as no surprise, as Jazz has failed to cite a single adverse event associated with the interaction between sodium oxybate and divalproex sodium arising in the fourteen (14) years the RLD has been on the market. Instead, Jazz is forced to engage in speculation about potential safety risks while eliding the twelve (12) years in which those risks did not manifest when the RLD carried the labeling now sought by generic applicants.

- The FDA administrative precedent cited by Jazz in the Citizen Petition shows that, if applicable to the current proceeding at all, it supports a conclusion opposite to the one Jazz would have FDA make. Each of the cited proceedings involved actual, not theoretical, safety risks and related to the carve-out of labeling statements included at the direction of FDA – not the NDA holder, as is the case here.

➢ Jazz's treatment of the REMS for the RLD is misleading, since Jazz ignores the fact that the language on divalproex sodium in the REMS supporting documents did not appear for almost a year after Jazz's approval of the labeling amendment on the issue, indicating that the safety concerns cited by Jazz are only relevant to the company insofar as they can be used as a tool to block generic competition and protect its market monopoly. Further, the mentions of divalproex sodium in the REMS supporting documents have no relation to the actual, clearly defined safety issues addressed by the REMS.

In sum, the Citizen Petition represents a quintessential example of a life-cycle management strategy employed with increasing frequency by NDA holders to avoid generic competition. The Citizen Petition plainly evidences market-driven concerns in its attempt to secure exclusive marketing for Xyrem for an additional nine (9) years past Jazz's existing patent

protection, from 2024 to 2033. If the Citizen Petition is granted, it would amount to a 31-year monopoly. This thinly veiled effort to delay generic competition cannot stand. Par respectfully requests that FDA deny Jazz's petition and permit Par's proposed labeling carve-out consistent with the applicable statute, regulations, and Agency precedent.

I. Jazz's Citizen Petition Is Solely an Attempt to Delay Generic Competition

A. Jazz Saw Fit to Address the "Safety Issue" with Divalproex Sodium Only When It Served Jazz's Anti-Competitive Strategy

Depakote (divalproex sodium) was approved in 1983 and has been on the market in several forms since that time, with numerous generic divalproex sodium products approved. Divalproex sodium is associated with a black box warning regarding the risks of hepatotoxicity, pancreatitis, and fetal harm in pregnant women, and the drug also has a patient-directed Medication Guide.[1] Yet despite the extensive safety warnings, co-administration with Xyrem is not mentioned on divalproex sodium labeling. Xyrem was approved in 2002, nearly 20 years after the approval of Depakote, also with a Medication Guide, as well as a risk management program that was an FDA condition of approval. However, neither the Xyrem label (including the Medication Guide) nor the Xyrem risk management program contained any reference to divalproex sodium, not to mention any safety concerns attendant to its co-administration with sodium oxybate, at the time of approval.[2] Despite several revisions to the Xyrem labeling over the years, including revisions to the risk management program, there continued to be no mention of divalproex sodium in any part of the Xyrem labeling until 2014.[3]

Two events in the twelve (12)-year timeframe between the Xyrem approval and the divalproex sodium labeling change are particularly notable. First, in 2007, Congress passed the Food and Drug Administration Amendments Act ("FDAAA") with new FDA authority to require a REMS for a drug if necessary to ensure that the benefits of the drug outweighed its risks.[4] In 2008, FDA released a notice indicating that the Xyrem risk management program was considered a "deemed" REMS and would be governed under the new REMS statutory framework, requiring Jazz to submit a proposed REMS to FDA.[5] However, the ultimate Xyrem REMS was not finalized for seven (7) years, during which FDA "faced repeated, lengthy delays"

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[1] Depakote Prescribing Information (Rev. Feb. 2016), http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/018723s056lbl.pdf.

[2] Xyrem Prescribing Information (Rev. July 2002), http://www.accessdata.fda.gov/drugsatfda_docs/label/2002/21196lbl.pdf.

[3] Xyrem Prescribing Information (Rev. Nov. 2005), http://www.accessdata.fda.gov/drugsatfda_docs/label/2005/021196s005lbl.pdf; Xyrem Prescribing Information (Rev. Dec. 2012), http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021196s013lbl.pdf; Xyrem Prescribing Information (Rev. Apr. 2014), http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021196Orig1s019lbl.pdf.

[4] 21 U.S.C. § 355-1(a)(1).

[5] Identification of Drug and Biological Products Deemed to Have Risk Evaluation and Mitigation Strategies for Purposes of the Food and Drug Administration Amendments Act of 2007, 73 Fed. Reg. 16313, 16314 (Mar. 27, 2008).

from Jazz as it developed its patent portfolio for the Xyrem REMS single-pharmacy system.[6] The omission of divalproex sodium information from the risk management program throughout this timeframe was never a stated concern, which omission is telling given the length of time.

Second, in 2012, FDA released a drug safety communication "reminding healthcare professionals and patients that the combined use of Xyrem (sodium oxybate) with alcohol or central nervous system (CNS) depressant drugs can markedly impair consciousness and may lead to severe breathing problems (respiratory depression)."[7] As part of this safety alert, FDA announced the addition of a new contraindication in the Xyrem label against the use of Xyrem with alcohol (which already included contraindications against use of Xyrem with insomnia drugs), and strengthened warnings against the use of Xyrem with alcohol or CNS depressant drugs. Again, concomitant use with divalproex sodium (an anticonvulsant) was not a stated issue of concern for Jazz or the Agency.

It was not until 2014, after Xyrem had been approved and on the market alongside Depakote for twelve (12) years, that FDA approved a labeling amendment with information from Jazz's drug-drug interaction ("DDI") study on sodium oxybate and divalproex sodium. The apparent lack of any safety signal during that timeframe belies Jazz's purported safety rationale for the labeling change (and the Citizen Petition). Indeed, Jazz fails to cite a single adverse event report regarding a DDI issue with divalproex sodium in its 14 years of marketing Xyrem. Although the Citizen Petition cites FDA's website as describing the divalproex sodium labeling revision among other FDA-approved "Safety Labeling Changes,"[8] the divalproex sodium labeling was *not* mandated under the applicable safety labeling changes framework enacted alongside the REMS framework in FDAAA. Under the statute, the Agency can *require* that an NDA holder add certain information to its labeling if FDA "becomes aware of new safety information" relating to "a serious risk… associated with use of the drug."[9] Yet Jazz makes no mention of such an FDA requirement in the Citizen Petition—nor could it, since such safety labeling changes are contemplated only for the *Warnings and Precautions*, *Contraindications*, and *Adverse Reactions* sections of the labeling.[10]

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[6] As FDA has described, "Jazz's position that a single pharmacy is critical to the safe use of Xyrem has not been a consistent one. In 2009, Jazz submitted a supplemental NDA for a new indication for Xyrem for treatment of fibromyalgia in which it proposed to include multiple certified pharmacies. However, by early 2011, after FDA declined to approve the fibromyalgia indication, Jazz changed its position. By that time, Jazz has been granted several patents related to its single pharmacy distribution system." FDA Supplement Approval Letter to Jazz Pharmaceuticals. Re: NDA 21196/S-015 (Feb. 27, 2015), http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/021196Orig1s015ltr.pdf.

[7] FDA, "FDA Drug Safety Communication: Warning Against Use of Xyrem (sodium oxybate) with Alcohol or Drugs Causing Respiratory Depression" (Dec. 17, 2012), http://www.fda.gov/Drugs/DrugSafety/ucm332029.htm.

[8] Jazz Pharmaceuticals, Inc. Citizen Petition Re: Xyrem (sodium oxybate), Docket No. FDA-2016-P-2672 (Sept. 16, 2016) [hereinafter Jazz Petition], at 5, *citing* FDA, "Xyrem (Sodium Oxybate) Oral Solution: Detailed View: Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research (CDER)" (Apr. 2014), http://www.fda.gov/safety/medwatch/safetyinformation/ucm335569.htm.

[9] 21 U.S.C. §§ 355(o)(4)(A), 355-1(b)(3).

[10] *Id.* § 355(o)(4)(B)(i).

Jazz's timing with regard to the divalproex sodium labeling amendment is also telling. According to the Citizen Petition, Jazz conducted its DDI study in 2012, though the results were not published until December 2013. Yet Jazz did not immediately file a labeling amendment with FDA upon completion of the study. Instead, Jazz's first order of business was to secure patent protection for the use of sodium oxybate with divalproex sodium. On **March 15, 2013** and **April 29, 2013**, Jazz filed two method-of-use patents with the USPTO: the '302 patent and '306 patent, respectively.[11] Only after it filed patents protecting the DDI information did Jazz submit a labeling amendment to FDA on **June 18, 2013**.[12] Notably, neither Jazz nor FDA felt it was important to add the divalproex sodium information to the Xyrem risk management program at the time of the labeling change.

While Jazz claims in the Citizen Petition that the divalproex sodium labeling constitutes "safety information," the Petition fails to articulate any concrete safety risk to patients posed by Par's proposed carve-out. This makes sense, since Jazz was in no hurry to make the divalproex sodium labeling available to prescribers and patients as it would have been obligated to do with a true safety risk. Under FDA's long-standing labeling regulations, certain labeling changes based on "newly acquired information" may be implemented by an NDA holder immediately upon submitting such changes to the Agency (without waiting for approval).[13] These Changes Being Effected ("CBE") supplements can include labeling revisions "[t]o add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling," or "[t]o add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product."[14] Jazz's failure to submit a CBE supplement for the divalproex sodium labeling change shows its (accurate) evaluation that the information is not a significant safety measure. Instead, Jazz's priority was to ensure that the labeling change served its purpose of extending the patent protection for Jazz's highest-grossing product.[15] If any further proof of this motive is required, Jazz itself, in communications to its investors, described the divalproex sodium labeling change as one part of its "lifecycle management of Xyrem" in which Jazz seeks to "enhance and enforce [its] intellectual property rights" in developing product improvements.[16] These statements speak for themselves.

At bottom, the Citizen Petition demonstrates the lengths to which Jazz will go in order to secure an extra nine (9) years without generic competition for a cumulative 31 years of complete sodium oxybate market monopoly.

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[11] U.S. Patent No. 9,050,302 (filed Mar. 15, 2013); U.S. Patent No. 8,772,306 (filed Apr. 29, 2013).

[12] FDA Supplement Approval Letter to Jazz Pharmaceuticals Re: NDA 21196/S-019 (Apr. 11, 2014), http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/021196Orig1s019ltr.pdf.

[13] 21 C.F.R. § 314.70(c)(6)(iii).

[14] *Id.* § 314.70(c)(6)(iii)(A), (C).

[15] In the first quarter of 2014, Xyrem represented 65.5% of Jazz's net product sales. *See* Jazz Pharmaceuticals plc, Form 10-Q (May 8, 2014), at 28.

[16] *Id.*

B. The Citizen Petition Cites a Safety Issue That Does Not Exist in the RLD's Labeling or Clinical Practice

Despite its arguments to the contrary, Jazz's attempt to block generic competition is not supported by the labeling for the RLD or the clinical experience with the product. *First*, Jazz argues that "[t]he clinical importance of the protected divalproex DDI information is reflected by its placement in the Xyrem package insert."[17] In fact, divalproex sodium is discussed in three sections of the Xyrem label: *Dosage and Administration*, *Drug Interactions*, and *Clinical Pharmacology*. Notably, as discussed below, none of these labeling sections are intended to convey information related to the safe use of the product, a fact that unsurprisingly goes unmentioned in the Citizen Petition.

With respect to *Dosage and Administration*, Jazz attempts to enhance the significance of its divalproex sodium labeling by quoting an FDA guidance document to say that "DDI information is included in that section when it 'is essential for prescribing decisions.'"[18] However, Jazz mischaracterizes the guidance language. Instead of speaking to the importance of the divalproex sodium information by reason of its inclusion in the *Dosage and Administration* section of the Xyrem label, the guidance actually demonstrates the information's *lack* of relative importance based on its *lack* of inclusion in the safety-related areas of the label, such as *Warnings and Precautions* or *Contraindications*. The guidance states:

> Drug interaction information should typically appear in the DRUG INTERACTIONS and CLINICAL PHARMACOLOGY sections. If there is a subset of information that is essential for prescribing decisions, that subset of information can be distributed among several sections, including the BOXED WARNING, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and DOSAGE AND ADMINISTRATION sections.
>
> When drug interaction information ***rises to the level of a contraindication, or a warning or precaution that necessitates a dosage adjustment***, this information should be presented succinctly in the applicable section(s), with details in the DRUG INTERACTIONS section.[19]

This concept is further supported by FDA's guidance on warnings and precautions labeling, which states:

> The WARNINGS AND PRECAUTIONS section should briefly describe any known or predicted drug interactions ***with serious or otherwise clinically significant outcomes*** and cross-reference to

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[17] Jazz Petition, at 10.

[18] *Id.*, *quoting* FDA, *Guidance for Industry: Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements* (Feb. 2013) [hereinafter PLR Guidance], at 5.

[19] PLR Guidance, at 5 (citations omitted) (emphasis added).

> any more detailed information elsewhere in the labeling (e.g., DOSAGE AND ADMINISTRATION, DRUG INTERACTIONS, or CLINICAL PHARMACOLOGY sections).[20]

The guidance further confirms that:

> Adverse reactions that do not meet the definition of a serious adverse reaction, but are otherwise clinically significant because they have implications for prescribing decisions or patient management, should also be included in the WARNINGS AND PRECAUTIONS section.[21]

The guidance clarifies that an "adverse reaction that may lead to a potentially serious outcome unless the dosage or regimen is adjusted" is a type of adverse reaction that could be deemed "otherwise clinically significant" and therefore included in the WARNINGS AND PRECAUTIONS section.[22]

According to FDA guidance, then, the fact that divalproex sodium is mentioned in only the three sections of the Xyrem label noted above means the DDI information did not "rise[] to the level of a contraindication, or a warning or precaution" and was not considered by Jazz at the time it filed the amendment to be "otherwise clinically significant" from the perspective of patient safety. To be sure, Par acknowledges that this information may be relevant to a clinician, but that does not compel a conclusion that the lack of such information would render the product less safe or effective. In fact, based on the requests made by Jazz in the Citizen Petition, the *location* of that information on the Xyrem label is what matters, and indeed should be dispositive. Inclusion of references to divalproex sodium on the Xyrem label does not, by rote, mean that the information is necessary for the safe use of the product. If that were the case, the information would have been conveyed as a warning, precaution, or contraindication. It does not require a great leap in logic to speculate as to why Jazz is claiming a safety issue now, when it did not do so at the time it filed the labeling amendment.

Second, Jazz argues that "[o]mitting the divalproex DDI labeling would leave prescribers to rely solely on the general warning in section 5.1 of the Xyrem package insert about concurrent use of sodium oxybate with other CNS depressants," which Jazz finds insufficient because "[p]rescribing decisions based on this incorrect assumption would risk increased GHB exposure and associated adverse events."[23] However, Jazz fails to explain why such adverse events are to be expected now when they failed to materialize in the twelve (12) years Xyrem was on the market without its current divalproex sodium labeling. As discussed further below, this

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[20] FDA, *Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warnings Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format* (Oct. 2011), at 6 (emphasis added).

[21] *Id.* at 4.

[22] *Id.*

[23] Jazz Petition, at 11.

argument also fails to take into account the reality of prescribing decisions in the carve-out context, where physicians would be advised *not* to administer the two drugs together. Again, Jazz appears to have conjured up possible safety risks that lack any connection to the actual Xyrem patient population in an effort to protect its patent posture vis-à-vis sodium oxybate generics.

Third, Jazz states that "[s]everal aspects of the [elements to assure safe use ("ETASUs")] in the REMS are designed to mitigate the risks posed by the potential DDI with divalproex," and that any REMS excluding the divalproex sodium information "would lack these critical aspects of Xyrem's ETASU."[24] Thus, according to Jazz, despite the fact that Xyrem has been marketed with a risk management program since the day it was approved, and the fact that this risk management program failed to contain any mention of divalproex sodium for almost thirteen (13) years, the current Xyrem REMS ETASUs were somehow "designed to mitigate" the risks of a divalproex sodium drug interaction and are now "critical" to the REMS program. This is cognitive dissonance at its finest. As FDA knows, the statute requires FDA to carefully examine and define the safety risks that give rise to FDA's authority to require a REMS for a specific drug. Indeed, FDA is only permitted to require a REMS with ETASUs if it determines that the drug "is associated with a serious adverse drug experienced, [and] **can be approved only if, or would be withdrawn unless**, such [ETASUs] are required as part of such strategy to mitigate a specific serious risk listed in the labeling of the drug...."[25] To be sure, the "specific serious risk" underlying the REMS program for Xyrem is *not* the risk of a divalproex sodium DDI, but rather the serious risks denoted in the Xyrem label warnings regarding abuse of this Schedule III controlled substance and misuse with contraindicated substances such as sedative hypnotics and alcohol. Jazz distorts the truth by insisting that that the two statements on divalproex sodium in the Xyrem REMS supporting documents constitute fundamental elements of the program.

Finally, Jazz argues that "differing instructions across sodium oxybate package inserts and REMS would confuse patients, prescribers, pharmacists, and other caregivers," and that this issue is only addressed by the Xyrem label which "identif[ies] the interaction between sodium oxybate and divalproex."[26] However, Jazz fails to account for the fact that the Depakote label does not mention the Xyrem drug interaction (despite detailing other drug interactions), and the lack of congruence in labeling between the Xyrem and Depakote labels is clearly not a safety concern for the Agency. Jazz also disregards the numerous prior instances where FDA has approved generic products with labeling that differs from their respective RLDs, each of which would have certainly violated Jazz's alleged labeling consistency concern.[27] In such cases, labeling consistency did not take precedence over the FDA statutory and regulatory imperatives that permit *and encourage* generic approval. Again, Jazz has populated its Citizen Petition with

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[24] *Id.* at 6, 14.

[25] 21 U.S.C. § 355-1(f)(1) (emphasis added).

[26] Jazz Petition, at 15.

[27] As discussed below, to Par's knowledge, there are only two (2) precedent examples available where FDA denied a proposed generic labeling carve-out, compared to the many instances where FDA approved proposed carve-outs based on findings that they would not affect product safety for non-protected conditions of use.

arguments that are unmistakably disingenuous in their reach. FDA should decline to entertain this blatant attempt to delay generic competition.

II. Par's Proposed Labeling Carve-Out Is Permissible and Appropriate Under the Statute, Regulations, and Agency Precedent

A. Applicable Law and Administrative Precedent Supports Par's Labeling Approach

The labeling carve-out framework is well established under the Federal Food, Drug, and Cosmetic Act ("FDCA") and FDA's implementing regulations. Pursuant to this framework, an ANDA applicant may submit a statement in lieu of submitting a certification to a brand's method of use patent listed in the Agency's *List of Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book"). This section viii statement, as it is called, makes clear that the applicable method of use patent "does not claim a use for which the [ANDA] applicant is seeking approval."[28] The ANDA applicant accurately makes this statement by ensuring that its generic product labeling "does not include any indications that are covered by the use patent"—i.e., it carves out the protected method of use.[29] Further, although the generic product labeling "must be the same as the labeling approved for the [RLD]," this same-labeling requirement does not apply to "changes required… because the drug product and the [RLD] are produced or distributed by different manufacturers."[30] Accordingly, "[s]uch differences between the applicant's proposed labeling and labeling approved for the [RLD] may include… omission of an indication or other aspect of labeling protected by patent."[31] However, when generic product labeling differs from RLD labeling under the carve-out framework, FDA will refuse to approve the ANDA unless the labeling differences "do not render the proposed drug product less safe or effective than the [RLD] for all remaining, nonprotected conditions of use."[32] Thus, the material issue for FDA's consideration is whether, pursuant to this framework, Par's proposed labeling that omits the protected condition of use nonetheless ensures that its generic sodium oxybate product is safe and effective for the remaining, non-protected conditions of use (i.e., administering sodium oxybate *without* divalproex sodium). Par is confident that it is.

FDA has utilized the statutory carve-out framework in approving numerous generic products in the past—including in situations where the carved out language includes drug interaction information—each time finding that the generic product was *not* less safe or effective than the RLD for the remaining, non-protected conditions of use. For example, in approving ANDAs referencing Camptosar (irinotecan hydrochloride), FDA permitted generic applicants to carve out information in their labels regarding the approved combination use of irinotecan with 5-flurouacil and leucovorin which included "relevant dosage and administration instructions,

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[28] 21 U.S.C. § 355(j)(2)(A)(viii).

[29] 21 C.F.R. § 314.94(a)(12)(iii)(A).

[30] *Id.* § 314.94(a)(8)(iv).

[31] *Id.*

[32] *Id.* § 314.127(a)(7).

drug-drug interactions, warnings, and precautions."[33] FDA found that the *Dosage and Administration* section of the generic label would "include all of the information necessary for proper dosing for the *approved*... use" and concluded that the generic product would be safe and effective for the *labeled, non-protected* uses even though the dosing was higher than the dosing for the carved out use.[34] Notably, in approving the carve-out, FDA stated:

> [T]he labeling of generic irinotecan will be essentially the same as the labeling with which Camptosar was originally approved. Camptosar was safely marketed with only this labeling for approximately 4 years (before the supplement for the combination use as first-line therapy was approved) and, of course, continues to include this information in its labeling today.[35]

Similarly, in approving ANDAs referencing Prandin (repaglinide), FDA permitted generic applicants to carve out information in their labels regarding the approved combination use with metformin, including information in the *Clinical Pharmacology* and *Dosage and Administration* sections of the label, stating: "[I]f a patient needs combination therapy with metformin, that patient can take the innovator drug, consistent with Prandin's labeling."[36]

As was the case in these prior precedent examples, Par's proposed label for its generic sodium oxybate product will remain the same as the label approved and used for Xyrem for twelve (12) years, except for those changes necessitated by the fact that Par is a distinct manufacturer *who is not seeking approval for concomitant use of sodium oxybate with divalproex sodium*. Par's product, so labeled, will remain safe and effective for all remaining, non-protected conditions of use—i.e., sodium oxybate *without* concomitant use of divalproex sodium—which, as discussed above, still includes *all* warnings, precautions, contraindications, and adverse events detailed in the Xyrem label. While Jazz makes every attempt to convince FDA that prescribers will administer Par's sodium oxybate product and divalproex sodium together despite Par's labeling carve-out, FDA precedent makes clear that the Agency's evaluation of the carve-out must consider the safety of the generic product *as labeled*, not the safety of any "foreseeable use" outside the four corners of the generic label.[37] In this context,

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[33] FDA Response to Watson Laboratories, Inc. Citizen Petition Re: Camptosar (irinotecan hydrochloride), Docket No. FDA-2008-P-0069 (July 28, 2008) [hereinafter Camptosar Response], at 9.

[34] *Id.* at 10 (emphasis added). FDA also referenced its precedent for Capoten (captopril), which was affirmed in *Bristol Meyers Squibb v. Shalala*, 91 F.3d 1493 (D.C. Cir. 1996), stating: "[I]n *Bristol-Myers Squibb*, we approved generic captropril with labeling that excluded two protected indications and corresponding protected, indication-specific dosing information. We did so even though the dosing and administration for the approved generic use was twice as high as the dosing for the carved-out indication." *Id.* at 12.

[35] *Id.* at 10.

[36] FDA Response to Novo Nordisk, Inc. Citizen Petition Re: Prandin (repaglinide), Docket Nos. FDA-2008-P-0343 and FDA-2008-P-0411 (Dec. 4, 2008), at 13.

[37] *Sigma-Tau Pharmaceuticals, Inc. v. Schwetz*, 288 F.3d 141, 145, 147 (4th Cir. 2002) ("[T]he evidentiary basis for the agency's approvals must be the use for which the approvals are sought—that is, the use for which the generics are labeled."); *see also, e.g.*, FDA Response to MedImmune Oncology, Inc. Citizen Petition Re: Ethyol (amifostine), Docket No. 2006P-0410 (Mar. 13, 2008), at 9-10.

Par's sodium oxybate label will continue to include strong warnings against the use of sodium oxybate with potentially interacting agents, and if needed, FDA can permit additional minor labeling changes to make clear that concomitant use of divalproex sodium is not approved.[38] From this perspective, there is no question that Par's product will be safe and effective with labeling that provides for the administration of sodium oxybate *without* coadministration of divalproex sodium, making Par's proposed label both adequate and appropriate for approval under the Hatch-Waxman framework.

B. The Precedent Jazz Cites Is Either Distinguishable or Supportive of the Carve-Out in Question

In a hollow attempt to cite precedent in support of its Petition, Jazz references two cases where FDA did not permit the carve-outs in question—Colcrys (colchicine) and Rapamune (sirolimus). However, to Par's knowledge, these are the only public examples of FDA denying a carve-out on safety grounds. Jazz's Petition itself attests to this fact, since the third and final example Jazz cites—Skelaxin (metaxalone)—is one where FDA found the particular carve-out in question permissible. In fact, the Skelaxin precedent shows FDA initially refusing to permit the proposed carve-out and then, after further consideration, reversing course to permit generic applicants to exclude the protected information from their labels. Thus, Jazz appears to have cited the Colcrys and Rapamune cases simply because they were the only two carve-out denials available, not because they have any bearing on the proposed carve-out at issue here.[39] In any event, the facts of these cases differ widely from those at issue for sodium oxybate and are distinguishable in many respects.

First, Jazz contends that the present proceeding "mirrors" the Colcrys case in which FDA rejected a proposed labeling carve-out for DDI information between colchicine and concomitant P-glycoprotein ("P-gp") inhibitors or strong CYP3A4 inhibitors. Jazz even states that, "[i]f anything, the need to include the protected DDI information is even starker here" because with colchicine, the particular DDIs at issue "were at least generally known in the medical community prior to being included in the Colcrys package insert."[40] What the Citizen Petition fails to discuss is the background behind the Colcrys approval that makes Jazz's allusion to this precedent seem absurd. Prior to approval of Mutual Pharmaceutical Company, Inc.'s ("Mutual's") 505(b)(2) NDA for Colcrys, single-ingredient colchicine products were marketed unapproved drugs, and Mutual conducted its DDI studies *at FDA's request* in order to obtain

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[38] *See, e.g.*, FDA Response to Savient Pharmaceuticals, Inc. Citizen Petition Re: Oxandrin (oxandrolone), Docket No. 2005P-0383 (Dec. 1, 2006) [hereinafter Oxandrin Response], at 21; FDA Response to Sandoz, Inc. Citizen Petition Re: Lyrica (pregabalin), Docket No. FDA-2010-P-0087 (July 30, 2010), at 9-10; FDA Response to Cephalon, Inc. Citizen Petition Re: Treanda (bendamustine hydrochloride), Docket No. FDA-2015-P-3980 (Mar. 24, 2016), at 13-15.

[39] Other brand petitioners have had the same idea to cite the Colcrys and Rapamune precedents in support of their arguments against generic carve-outs, but FDA rejected the comparisons in each case. *See e.g.*, FDA Response to United Therapeutics Corp. Citizen Petition Re: Remodulin (trepostinil), Docket No. FDA-2013-P-1293 (Mar. 10, 2014), at 9-10; FDA Response to Mutual Pharmaceutical Company, Inc. Citizen Petition Re: Colcrys (colchicine), Docket No. FDA-2012-P-1018 (Feb. 15, 2013), at 10.

[40] Jazz Petition, at 12.

approval.[41] At the time, 169 deaths had been reported due to colchicine toxicity, 117 of which involved fatal drug interactions.[42] Thus, the medical community knew about the DDI issue prior to the Colcrys approval because unapproved colchicine products had been associated with life-threatening drug interactions reported in the medical literature.[43] Contrast these facts with the Xyrem situation, where sodium oxybate has been on the market for fourteen (14) years and Jazz cannot cite a single adverse event associated with a divalproex sodium drug interaction. With Colcrys, FDA also mandated the specific DDI testing as a *prerequisite to approval* for safety reasons, but with Xyrem, Jazz took it upon itself to initiate the divalproex sodium labeling change as part of its "lifecycle management" strategy for the product, a change that was not made in response to a conditioned requirement for FDA approval. Moreover, unlike with Xyrem, the Colcrys drug interaction rose to the level of a contraindication and was accordingly included in the *Warnings and Precautions* and *Contraindications* sections of the label, among other sections,[44] a circumstance which is not the case with the Xyrem labeling. The facts of the Colcrys case are obviously not comparable to those at issue with Xyrem, making this precedent distinguishable in FDA's consideration of the labeling carve-out here.

Similarly, Jazz also cites FDA's denial of a generic labeling carve-out for ANDAs referencing Rapamune as relevant because, like FDA found with Rapamune, the "protected labeling is necessary for prescribers to titrate or individualize patients'… therapy."[45] However, again, Jazz fails to provide the whole story. Similar to Colcrys, the DDI information obtained by the Rapamune NDA holder (here, Wyeth Pharmaceuticals ("Wyeth")) was associated with studies *required by FDA* as post-approval commitments. In particular, when Rapamune was approved, it was intended for administration in combination with cyclosporine and corticosteroids, and FDA required Wyeth, among other conditions of approval, to continue assessing the drug regimen's effect on renal function based on safety concerns identified in the initial clinical program.[46] Within this context, Wyeth conducted a study supporting a cyclosporine withdrawal regimen that formed the protected labeling information at issue.[47] Wyeth then submitted the relevant labeling change less than two years after the Rapamune approval, adding "[e]xtensive information… including [to] the *Pharmacokinetics*, *Clinical Studies*, *Indications and Usage*, *Warnings*, *Precautions*, and *Adverse Reactions* sections of the

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[41] Mutual Pharmaceutical Company, Inc. Citizen Petition Re: Colcrys (colchicine), Docket No. FDA-2010-P-0614 (Nov. 26, 2010), at 1.

[42] *Id.*, at 6.

[43] FDA Response to Mutual Pharmaceutical Company, Inc. Citizen Petition Re: Colcrys (colchicine), Docket No. FDA-2010-P-0614 (May 25, 2011), at 19.

[44] Colcrys Prescribing Information (Rev. July 2009), http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022351lbl.pdf.

[45] Jazz Petition, at 12-13.

[46] FDA Approval Letter to Wyeth Pharmaceutical Re: NDA 21083 (Sep. 15, 1999), http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/21083A_Rapamune_appltr.pdf, at 2.

[47] FDA Response to Wyeth Pharmaceuticals Citizen Petition Re: Rapamune (sirolimus), Docket No. 2003P-0518 (Sep. 20, 2004), at 1.

labeling."[48] Again, the facts of this precedent fail to line up with those at issue for Xyrem, where the divalproex sodium labeling was added on Jazz's initiative more than a decade after approval of the product and, in any event, never rose to the level of a warning on FDA's radar. Moreover, FDA has a history of approving generic labels carving out titration schedules in situations where it determined that doing so would not render the generic products less safe for their labeled, non-protected uses.[49] Again, the factual distinctions of this cited precedent make Jazz's attempted comparisons in this context misplaced.

Finally, Jazz references FDA's "carve-out dilemma" for Skelaxin regarding statements in the *Precautions* section of the label that taking the drug with food may enhance general CNS depression, especially in elderly patients. Jazz cites to an FDA statement that "[c]arving out patent-protected language from the Precautions section of a label that pertains to a labeled use would generally not be permitted,"[50] and Jazz likens the situation to Xyrem to emphasize "[t]he rule against carving out warnings or precautions."[51] It seems to be lost on Jazz that this comparison is actually hurtful to its Petition in speaking to the *Warnings and Precautions* section of the Skelaxin label, when the divalproex sodium information notably does *not* appear in that section of the Xyrem label. More importantly, however, Jazz fails to disclose that FDA actually permitted the particular carve-out in question when the language was initially included in the *Clinical Pharmacology* section of the Skelaxin label. As detailed in King Pharmaceuticals, Inc.'s ("King's") citizen petition on the issue:

> Initially, FDA took the position that pharmacokinetic information describing the relative bioavailability of metaxalone when taken with or without food, as reflected in the current approved SKELAXIN® label, must be included in the labeling for generic versions of SKELAXIN®, and required generic applicants to file [paragraph IV] patent certifications.... On March 9, 2004, King received [a] 'Dear Applicant' letter dated March 1, 2004, from the FDA explaining that it was reversing its position and inviting ANDA applicants to file section (viii) statements against the listed patents rather than paragraph IV certifications. FDA stated in its March 1, 2004 Letter that pharmacokinetic information describing the relative bioavailability of metaxalone when taken with or

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[48] *Id.* at 2.

[49] *E.g.*, FDA Response to Apotex Corp., Teva Pharmaceutical USA, and Caraco Pharmaceutical Laboratories, Ltd. Citizen Petitions Re: Ultram (tramadol), Docket Nos. 01P-0495, 02P-0191, and 02P-0252 (June 11, 2002), at 8-10.

[50] Jazz Petition, at 13, *quoting* Letter from Martin Shimer Re: Background for Sandoz Metaxalone Tablets, 800 mg; Decision Regarding Non-Forfeiture of 180-Day Exclusivity (Mar. 29, 2010) [hereinafter Metaxalone Exclusivity Letter].

[51] *Id.*

> without food, as reflected in the current approved SKELAXIN® label, could be omitted from the labeling for generic metaxalone.[52]

Notably, in the referenced FDA "Dear Applicant" letter, the Agency highlighted the fact that the labeling information at issue did not "result in any changes to the warnings, precautions or contraindications in the Skelaxin labeling."[53] More than two years after this letter, FDA approved an additional labeling supplement from King which added additional food effect information to the *Precautions* section of the label,[54] but FDA never formally decided the issue of whether ANDA applicants could still carve out this information—as Jazz acknowledges, the applicable patent was found to be invalid in litigation, obviating any need for the carve-out.[55] However, this is of no consequence, since the particular Xyrem labeling information at issue here is clearly *not* in the *Warnings and Precautions* section and has never risen to that level in fourteen (14) years. Thus, the Skelaxin precedent, like the others, shows only how frivolous Jazz's petition is in attempting to convince the Agency that the situation here is anything other than an effort to delay generic competition.

III. Par's Proposed Labeling Carve-Out Is Not a REMS Issue

A. Par's Proposed Carve-Out Properly Encompasses All Labeling, Including REMS Labeling

As noted above, the REMS framework was enacted in 2007 to enable access to drugs for which a risk mitigation strategy was "necessary to ensure that the benefits of the drug outweigh the risks of the drug."[56] This framework was passed as part of a suite of legislation that provided FDA with new post-marketing authorities, including being able to require sponsors to conduct post-approval clinical trials and make FDA-mandated safety labeling changes (again, Jazz's divalproex sodium labeling change was *not* mandated by FDA under these authorities).[57] These statutory provisions all formally enacted certain powers that FDA was partially exercising in other ways prior to their enactment, including requiring companies to develop a risk mitigation strategy as a condition of approval. This was the case with Xyrem.

Xyrem was initially approved with a risk management program directed at the drug's Schedule III controlled substance status for potential misuse as a "date rape" drug.[58] This significant safety risk continues to be the primary focus of the Xyrem REMS. Indeed, co-

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[52] King Pharmaceuticals, Inc. Citizen Petition Re: Skelaxin (metaxalone), Docket No. 2004P-0140 (Mar. 18, 2004) [hereinafter King Petition], at 9-10.

[53] Letter from Gary J. Buehler Re: ANDA for Metaxalone Tablets (Mar. 1, 2004) (attachment 6 to King Petition).

[54] King Petition Supplement, Docket No. 2004P-0140 (Feb. 13, 2007), at 6-7.

[55] Metaxalone Exclusivity Letter.

[56] 21 U.S.C. § 355-1(a)(1).

[57] *Id.* § 355(o)(3)-(4).

[58] The *Warnings and Precautions* section of the Xyrem label provides: "The rapid onset of sedation, coupled with the amnestic features of Xyrem, particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary user (e.g., assault victim)." Xyrem Prescribing Information (Rev. Apr. 2014), at § 5.2.

administration of sodium oxybate with divalproex sodium has *never* been the focus of the Xyrem risk management framework—it was never mentioned in the pre-REMS program, including for almost a year after FDA approved the relevant change to the Xyrem Prescribing Information. In 2015, FDA formally approved a REMS for Xyrem under Section 505-1 of the FDCA, but divalproex sodium is *still* not mentioned in the main "REMS Document." Instead, that document states that the "goal" of the Xyrem REMS is "to mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion,"[59] and to do so, the system will "[i]nform prescribers, pharmacists, and patients of… [t]he contraindication of use of XYREM with sedative hypnotics and alcohol."[60] The REMS Document also states that the system will "[e]nsur[e] that pharmacy controls exist prior to filling prescriptions for XYREM that… [s]creen for concomitant use of sedative hypnotics and other potentially interacting agents," and "[n]otify prescribers when patients are receiving concomitant contraindicated medications or there are signs of potential abuse, misuse, or diversion."[61] Thus, to the extent the REMS focuses on use of sodium oxybate with other products, that focus is directed at the contraindicated products discussed in the *Warnings and Precautions* and *Contraindications* sections of the Xyrem label.

When the Xyrem REMS was approved in 2015, the program included two supporting documents with one line each on divalproex sodium—the physician-directed Xyrem Prescriber Brochure and the pharmacy-directed Patient Counseling Checklist. However, the Prescriber Brochure only copies the same DDI information from the Xyrem label in a section titled "Dosing Xyrem."[62] The Patient Counseling Checklist likewise simply directs pharmacists to ask if the relevant patient is taking any of the listed contraindicated or potentially interacting substances, including "anti-epileptics such as divalproex sodium (Depakote)."[63] However, the full Xyrem REMS comprises 91 pages, 89 of which do not contain any mention of divalproex sodium (including the entire patient-directed Medication Guide). As discussed above, the fact that divalproex sodium is briefly mentioned in two REMS supporting documents does not transform the DDI information into a "specific serious risk" to be addressed by the Xyrem REMS. Rather, it seems obvious that in keeping with its "lifecycle management" approach, Jazz sought to add the divalproex sodium information to the Xyrem REMS to further enhance the scope of its patent protection. As such, removing this information to effectuate a generic labeling carve-out cannot raise new safety concerns that were not present for the initial twelve (12) years of Xyrem marketing, or the additional year in which Xyrem was marketed with divalproex sodium labeling that lacked corresponding language in the REMS.

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[59] Xyrem REMS Document (Rev. June 2015), http://www.accessdata.fda.gov/drugsatfda_docs/rems/Xyrem_07-15-2015_REMS_document.pdf, at § I.

[60] *Id.*

[61] *Id.*

[62] Xyrem REMS Prescriber Brochure (Rev. June 2015), http://www.accessdata.fda.gov/drugsatfda_docs/rems/Xyrem_07-15-2015_Prescriber_Brochure.pdf, at 10.

[63] Xyrem REMS Patient Counseling Checklist (Rev. June 2015), http://www.accessdata.fda.gov/drugsatfda_docs/rems/Xyrem_07-15-2015_Patient_Counseling_Checklist.pdf, at 5.

More to the point, the primary issue for consideration by the Agency in this context is whether Par's proposed label meets the statutory and regulatory requirements for a section viii carve-out. If FDA concludes that these requirements are met—as the discussion above demonstrates that it should—then FDA can approve the carve-out throughout *all* of Par's labeling, including the REMS. Nothing in the REMS statute indicates that it was meant to abrogate the section viii carve-out framework, and FDA has authority to implement the framework accordingly here. In fact, Par is unaware of any circumstance in which FDA has denied a proposed generic labeling carve-out on the *sole* grounds that the labeling information at issue was repeated in the RLD's REMS. The intent behind the Hatch-Waxman carve-out provision counsels that this should continue to be the case. In this respect, FDA is empowered to "enabl[e] the marketing of lower-cost, generic versions of... drugs at the earliest possible time" with labeling that ensures safety for *non-protected* conditions of use.[64] Accordingly, FDA has both the authority and mandate to approve Par's proposed generic labeling carve-out here.

B. Language in REMS Supporting Documents Regarding Concomitant Use of Divalproex Sodium Is Not an ETASU

In the Citizen Petition, Jazz alludes to the REMS statute provision which states that, if FDA grants a waiver from the requirement for an ANDA applicant to "use a single, shared system" with the brand, the waiver-granted REMS must "use a different, comparable aspect of the [ETASUs]."[65] Jazz cites this language to claim that if ANDA applicants are permitted to carve out the divalproex sodium information from their REMS materials, "[t]hese aspects of their REMS ETASU would not be comparable to Xyrem's, which means their ANDAs would not be approvable."[66] But here, Jazz confuses the word "comparable" with "identical." Clearly, as is the case with permissible label changes based on different manufacturers, REMS labeling changes can likewise be implemented to account for different manufacturers while *still* being comparable to the brand REMS. However, this fact is ultimately immaterial, since the minimal divalproex sodium information in the Xyrem REMS certainly does not constitute an aspect of any ETASU that must be "comparable" under the statute.

In the statutory section Jazz references, Congress made clear that an ANDA product is only subject to limited, enumerated REMS requirements applicable to the RLD, including: (1) a Medication Guide or patient package insert, and (2) ETASUs.[67] With respect to the latter requirement, the statute provides that an ANDA product and its RLD "shall use a single, shared system" for ETASUs; however, FDA may waive this requirement "and permit the [ANDA] applicant to use a different, comparable aspect of the [ETASUs]" if FDA makes certain findings.[68] The question of whether FDA can approve a waiver from the requirement for a

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[64] Camptosar Response, at 14.

[65] 21 U.S.C. § 355-1(i)(1)(B).

[66] Jazz Petition, at 13.

[67] 21 U.S.C. § 355-1(i)(1)(A)-(B).

[68] FDA may grant a waiver if it finds that (1) "the burden of creating a single, shared system outweighs the benefit of a single, [shared] system, taking into consideration the impact on health care providers, patients, the [ANDA applicant], and the [RLD] holder"; or (2) "an aspect of the [ETASU] for the [RLD] is claimed by a patent... or is

single, shared REMS system for proposed generic products is not the subject of the Citizen Petition and is, accordingly, not appropriate for consideration here. However, to the extent Jazz's assertions implicate this issue, they do so in a way that mischaracterizes the nature of ETASUs as contemplated by the statute.

To be clear, ETASUs can include only specific enumerated requirements with respect to health care providers prescribing the drug, pharmacies or other health care settings dispensing the drug, and patients receiving the drug. In particular, an ETASU may require: (1) that prescribers "have particular training or experience, or are specially certified"; (2) that dispensers likewise be "specially certified"; and/or (3) that patients receive the drug "only in certain health care settings," have "evidence or other documentation of safe-use conditions, such as laboratory test results," "be subject to certain monitoring," or "be enrolled in a registry."[69] Under the Xyrem REMS, accordingly, both Xyrem prescribers and the central pharmacy are specially certified pursuant to the training requirements outlined in the REMS, and Xyrem is dispensed only to patients who are enrolled in the REMS program.[70] However, although the contemplated certifications in the REMS involve use of the Xyrem Prescriber Brochure and Patient Counseling Checklist, the fact that divalproex sodium is mentioned in these documents does not transform the language into an "aspect of the ETASU"—to the contrary, the ETASU "aspects" contemplated under the statute embody the overall documents themselves. As a result, any *non-essential* language included in these documents cannot be considered necessary "aspects" that must be "comparable" to the RLD REMS. Indeed, if Jazz removed the divalproex sodium language from the applicable documents, it would have *no material effect* on the actual ETASUs or administration of the program. In light of this fact, Par's proposed labeling carve-out should have no bearing on the Agency's evaluation of a potential waiver. Jazz's assertions to the contrary only further demonstrate its anti-competitive intent, contrary to the express prohibition in the statute against RLD holders "us[ing] any [ETASU]… to block or delay approval of an [ANDA]."[71]

IV. Decades of Hatch-Waxman Policy Supports Agency Approval of Par's Proposed Labeling Carve-Out

In the final rule enacting regulations implementing the Hatch-Waxman carve-out framework, FDA explained that "a patent may be a valid reason for labeling differences between the [RLD] and the ANDA drug product and… such differences should not be a basis for refusing to approve an ANDA."[72] Although FDA cautioned that it "will not approve an ANDA with different labeling if the labeling differences affect product safety or efficacy,"[73] FDA's track record of approving generic products with carved out labeling has shown that this is rarely the

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a… trade secret… and the [ANDA applicant] certifies that it has sought a license… and that it was unable to obtain a license." 21 U.S.C. § 355-1(i)(B)(i)-(ii).

[69] *Id.* § 355-1(f)(3).

[70] Xyrem REMS Document (Rev. June 2015), at § II. B.

[71] 21 U.S.C. § 355-1(f)(8).

[72] Abbreviated New Drug Application Regulations; Final Rule, 57 Fed. Reg. 17950, 17968 (Apr. 28, 1992).

[73] *Id.*

case. Indeed, in approving numerous carve-outs over the years, FDA has consistently cited the need to honor the "balance" struck by Hatch-Waxman that "allows the innovator and associated patent holders to enjoy the benefits associated with their research… [while] promot[ing] generic competition for the remaining, non-protected condition[s] of use for which the [RLD] is approved."[74] In a recent final rule, FDA made additional changes to its Hatch-Waxman regulations in order to "facilitate FDA's implementation" of the carve-out framework,[75] thereby further encouraging its use as a pro-competitive path to market for generic products.

Par's proposed sodium oxybate labeling carve-out is precisely the type of scenario in which this overarching Hatch-Waxman policy was meant to apply. Jazz has already enjoyed fourteen (14) years of sodium oxybate monopoly and, excluding the divalproex sodium labeling protection, stands to enjoy an additional eight (8) years more.[76] The difference between permitting Par's proposed labeling carve-out and denying it means a difference of nine (9) additional years of exclusive marketing for Xyrem—a total of 31 years when Jazz's '302 and '306 patents expire on March 15, 2033.[77] Such an extreme delay in generic competition on account of Jazz's transparent evergreening strategy cannot stand under Hatch-Waxman, especially in the face of a proposed generic labeling carve-out that will have no impact on the safety of sodium oxybate for non-protected conditions of use.

As discussed at length above, Jazz's divalproex sodium labelling change did not stem from a serious safety signal and was never focused in the key safety sections of the Xyrem label. Jazz's corresponding additions to the Xyrem REMS were likewise motivated by patent concerns, and in any event, have no bearing on the actual, serious safety risks addressed by the REMS program. Par's sodium oxybate labeling will continue to include strong warnings against the use of sodium oxybate with potentially interacting agents, and if needed, FDA can permit additional minor labeling changes to make clear that concomitant use of divalproex sodium is not approved. With these facts, FDA has ample authority to approve the proposed labeling carve-out for Par's generic sodium oxybate product. FDA should deny Jazz's petition in full.

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[74] FDA Response to Valeant Pharmaceuticals International Citizen Petition Re: Rebetol (ribavirin), Docket No. 2003P-0321 (Apr. 6, 2004), at 31; *see also, e.g.*, Oxandrin Response, at 20; Camptosar Response, at 14; FDA Response to Unimed Pharmaceuticals, Inc. Citizen Petition Re: Marinol (dronabinol), Docket No. FDA-2007-P-0169 (Apr. 25, 2008), at 10; FDA Letter to NDA and ANDA Applicants Re: Precedex (dexmedetomide hydrochloride), Docket No. FDA-2014-N-0087 (Aug. 18, 2014), at 13.

[75] Abbreviated New Drug Applications and 505(b)(2) Applications; Final Rule, 81 Fed. Reg. 69580, 69580 (Oct. 6, 2016).

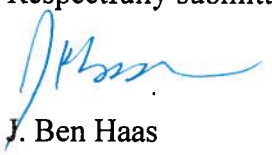
[76] Orange Book Patent Listings for NDA No. 21-196, http://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=021196&Appl_type=N

[77] *Id.*

Verification

I certify that, to my best knowledge and belief: (a) I have not intentionally delayed submission of this document or its contents; and (b) the information upon which I have based the action requested herein first became known to me on or about October 1, 2016. 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: Par Pharmaceutical, Inc. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,



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