

**MEMORANDUM**

DATE: January 17, 2017

TO: Abbreviated New Drug Applications (ANDAs) for sodium oxybate oral solution products

ANDA 202090 - Roxane Laboratories, Inc. (Roxane)

(b) (4)

ANDA 203351 - Ohm Laboratories, Inc. (Ohm)

ANDA 203631 - Amneal Pharmaceuticals (Amneal)

(b) (4)

THROUGH

Senior Regulatory Counsel  
Office of Regulatory Policy

FROM: Trueman W. Sharp, M.D., M.P.H.

Deputy Director  
Office of Bioequivalence  
Office of Generic Drugs

SUBJECT: Decision to waive the requirement for a single, shared system REMS for sodium oxybate oral solution

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**Executive Summary**

This memorandum explains the Food and Drug Administration's (FDA's or the Agency's) decision to waive the requirement for a single, shared system (SSS) risk evaluation and mitigation strategy (REMS) for sodium oxybate oral solution drug products (sodium oxybate). Each applicant listed above currently has pending an abbreviated new drug application (ANDA) referencing Xyrem (sodium oxybate) Oral Solution (Xyrem), a product marketed under a new drug application (NDA) held by Jazz

Pharmaceuticals (Jazz), as the reference listed drug (RLD). Xyrem is approved with a REMS that includes elements to assure safe use (ETASU).<sup>1</sup>

Section 505-1(i)(1)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) requires that a generic drug (e.g., sodium oxybate) and the applicable listed drug (e.g., Xyrem) must use an SSS if a REMS with ETASU is required for the listed drug. It also gives FDA the authority to waive this requirement if the Agency determines that the burden of creating an SSS outweighs its benefit, taking into account the impact on the relevant stakeholders, or if an ANDA applicant certifies that it sought a license for use of an aspect of the applicable listed drug's ETASU claimed by a patent that has not expired or a method or process that, as a trade secret, is entitled to protection, and was unable to obtain one.<sup>2</sup> As explained in more detail below, although either ground would be sufficient on its own, FDA finds that both prongs of this standard have been met for sodium oxybate: the burden of creating an SSS for these products outweighs the benefit, and (b) (4) ANDA (b) (4) certified that (b) (4) sought a license for use of an aspect of Jazz's ETASU claimed by a patent and were unable to obtain one. Accordingly, the Agency has determined to waive the SSS requirement.

The ANDA (b) (4) proposed REMS<sup>3</sup> has the same ETASU as those in the Xyrem REMS. Specifically, both the Xyrem REMS and the proposed sodium oxybate ANDA REMS require that: (1) healthcare providers who prescribe the drug are specially certified<sup>4</sup>; (2) the drug will be dispensed only by pharmacies that are specially certified<sup>5</sup>; and (3) the drug will be dispensed and shipped only to patients who are enrolled in the REMS program with documentation of safe use conditions.<sup>6</sup> Although *aspects* of these requirements in the proposed sodium oxybate REMS vary because of differences in how the ETASU will be operationalized (e.g., the use of multiple, certified pharmacies rather than a single pharmacy), FDA has further determined that the different aspects of the

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<sup>1</sup> See section 505-1 of the FD&C Act. The currently approved Xyrem REMS can be found on the FDA's Approved REMS website: <http://www.accessdata.fda.gov/scripts/cder/remis/index.cfm>. The single shared system requirement applies if the REMS for the applicable listed drug includes elements to assure safe use. For ease of reference in this memorandum, however, we refer to an SSS for the ETASU portion of a REMS as a "single, shared system REMS" or simply "single, shared system[.]"

<sup>2</sup> See section 505-1(i)(1)(B) of the FD&C Act.

<sup>3</sup> (b) (4) the ANDA (b) (4) submitted a REMS amendment for a proposed shared ANDA REMS on April 8, 2016 or April 11, 2016, and (b) (4) submitted a subsequent amendment on December 2, 2016. The shared ANDA REMS discussed in this memorandum refers to the proposed shared ANDA REMS submitted on December 2, 2016. Contemporaneous with this memo, FDA is approving the ANDA submitted by Roxane (202090) with the ANDA REMS submitted on December 2, 2016. (b) (4)

See section 505-1(f)(3)(A) of the FD&C Act.

<sup>5</sup> See section 505-1(f)(3)(B) of the FD&C Act.

<sup>6</sup> See section 505-1(f)(3)(D) of the FD&C Act.

ETASU in the REMS proposed by the ANDA (b) (4) described above are comparable to those in the Xyrem REMS.

To help assure that this decision does not unduly burden health care providers, patients, or the U.S. healthcare system in general, FDA is attaching a condition to the waiver: that the ANDA (b) (4) waiver-granted REMS system be open to all future applicants of sodium oxybate products.

The remainder of this memorandum provides a summary of relevant background information and explains in further detail the Agency's rationale for waiving the requirement for an SSS REMS for sodium oxybate and for determining that the differences in the way the ETASU in the ANDA REMS are operationalized are comparable to the corresponding aspects of the ETASU in the Xyrem REMS.

## **I. The Statutory Standard**

The Agency's authority to waive the requirement for an SSS REMS is governed by section 505-1(i)(1)(B) of the FD&C Act. In relevant part, section 505-1(i)(1)(B) states:

The Secretary may waive the [SSS REMS requirement] for a drug that is the subject of an abbreviated new drug application, and permit the applicant to use a different, comparable aspect of the elements to assure safe use, if the Secretary determines that—

- (i) the burden of creating a single, shared system outweighs the benefit of a single, system, taking into consideration the impact on health care providers, patients, the applicant for the abbreviated new drug application, and the holder of the reference drug product; or
- (ii) an aspect of the elements to assure safe use for the applicable listed drug is claimed by a patent that has not expired or is a method or process that, as a trade secret, is entitled to protection, and the applicant for the abbreviated new drug application certifies that it has sought a license for use of an aspect of the elements to assure safe use for the applicable listed drug and that it was unable to obtain a license.

Thus, FDA has explicit legal authority to waive the requirement that the RLD and an ANDA that references the RLD use an SSS for the ETASU portion of a REMS, provided

the Agency determines either that the burden of creating an SSS REMS outweighs the benefit of such an SSS REMS (taking into account the impact on the statutorily-identified stakeholders) or that the ANDA applicant certifies that it sought a license for use of an aspect of the ETASU claimed by a patent and was unable to obtain one.

## **II. Background**

### **A. Xyrem (sodium oxybate) Oral Solution**

On July 17, 2002, FDA approved NDA 21-196 for Xyrem for the treatment of cataplexy in patients with narcolepsy, and on November 18, 2005, FDA approved a supplemental new drug application (sNDA) for Xyrem for the treatment of excessive daytime sleepiness in patients with narcolepsy.

The prescription drug Xyrem is the sodium salt of gamma-hydroxybutyrate (GHB). GHB is a Schedule I controlled substance, while FDA-approved products containing GHB (including its salts, isomers, and salts of isomers), including Xyrem (sodium oxybate), are controlled under Schedule III.<sup>7</sup> Risks associated with Xyrem at recommended doses can include central nervous system (CNS) depression, respiratory depression, confusion, and neuropsychiatric events (such as depression). Abuse of GHB either alone or in combination with other CNS depressants is associated with adverse reactions including seizure, respiratory depression, decreases in the level of consciousness, coma, and death. The rapid onset of sedation, coupled with amnesia, particularly when combined with alcohol, poses risks for voluntary and involuntary users (e.g., assault victims).

### **B. The Xyrem REMS**

The Xyrem REMS requires distribution of a Medication Guide in accordance with 21 CFR Part 208. The REMS also requires ETASU to mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion of Xyrem.<sup>8</sup> Prior to filling a Xyrem prescription, the pharmacy must screen for a patient's concomitant use of sedative-hypnotics and other potentially interacting agents, monitor for inappropriate prescribing, misuse, abuse, and diversion, and notify prescribers when patients are receiving concomitant contraindicated medications or there are signs of

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<sup>7</sup> 21 CFR 1308.11(e)(1) and 1308.13(c)(6).

<sup>8</sup> As explained in the 2015 Xyrem REMS approval letter, the goal of mitigating "diversion" in this REMS refers to preventing the sale or transfer of the drug outside the framework of the REMS in order to mitigate the risks of central nervous system depression, respiratory depression, abuse, and misuse. Supplement 15 Approval Letter at 2 (Feb. 27, 2015).

potential abuse, misuse, or diversion. In addition, the REMS is designed to mitigate the risks by informing prescribers, pharmacists, and patients of the risk of significant central nervous system and respiratory depression associated with Xyrem, the contraindication of use of Xyrem with sedative-hypnotics and alcohol, the potential for abuse, misuse, and overdose associated with Xyrem, and the safe use, handling, and storage of Xyrem.

Finally, the Xyrem REMS also includes an implementation system through which the sponsor evaluates and monitors compliance with the REMS requirements, as well as a timetable for the submission of REMS assessments.

### **C. Relevant Regulatory History**

The chronology of primary importance in FDA's determination to grant a waiver in this case is the history of discussions between Jazz and the ANDA <sup>(b) (4)</sup> regarding the development of an SSS. However, because the content and structure of the Xyrem REMS inevitably affects the contours of an SSS or a separate, waived system, the history of the establishment and evolution of the Xyrem REMS – including the roughly seven years of discussions and disagreements between FDA and Jazz about the REMS – is also described below. These two chronologies have proceeded in parallel from approximately 2012 to the present.

#### **1. History of Xyrem REMS**

Xyrem was originally approved in 2002 under the restricted distribution regulations contained in 21 CFR 314.500 (Subpart H) with a risk management plan to assure safe use of the product. The original risk management plan proposed by Jazz contained a requirement that the drug be dispensed only from a single, central pharmacy. FDA approved the plan with this limitation, believing it to be a good way to effectuate the overall restrictions on distribution necessary for safe use of the drug.<sup>9</sup>

Under Section 909 of the FDA Amendments Act (FDAAA), which was enacted in 2007, a drug that was approved before the effective date of FDAAA was deemed to have in effect an approved REMS if there were in effect on the effective date of FDAAA elements to assure safe use required under section 314.520 of FDA regulations. Sponsors of these products, which included Xyrem, were required to submit a proposed REMS to FDA by September 21, 2008 (FDAAA Section 909(b)(3)). Jazz submitted such a proposal on August 29, 2008. That proposal was amended multiple times by Jazz.

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<sup>9</sup> See REMS modification notification letter, December 20, 2013.

In August 2009, as part of its transition from a risk management plan to a REMS, Jazz submitted a proposal to, among other things, remove the restriction to a single pharmacy and instead allow certification of multiple pharmacies. Its rationale for this proposed change was that it would “increase patient access without compromising patient safety.”<sup>10</sup> Jazz also stated that the single pharmacy program in existence at that time “imposes numerous impediments to patient access to Xyrem, possibly depriving narcolepsy patients of an important medication to control their EDS and cataplexy and potentially affect their lives dramatically.”<sup>11</sup> Later that year Jazz also submitted a new NDA (22-531) seeking approval for a new indication for fibromyalgia, and in that application proposed a REMS with multiple certified pharmacies. FDA declined to approve the application for fibromyalgia, but did so on grounds unrelated to the multiple pharmacy certification.<sup>12</sup>

After FDA declined to approve the Xyrem fibromyalgia application, discussions between FDA and Jazz regarding the REMS for Xyrem continued. In early 2011, Jazz changed its position and abruptly dropped its proposal for certification of multiple pharmacies. By that time, Jazz had listed several patents related to its REMS in FDA’s *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book).

In August 2012, FDA provided interim comments on the proposed REMS which stated that, consistent with Jazz’s earlier request, the final REMS should not contain the single pharmacy limitation, but should instead include the same stringent requirements as part of the requirements for pharmacy certification.<sup>13</sup> FDA, considered, among other things, the statutory requirement under the FD&C Act that ETASU be imposed only if “necessary to assure safe use of the drug,”<sup>14</sup> that ETASU be “commensurate with the specific serious risk[s] listed in the labeling” of the drug, that ETASU “not be unduly burdensome on patient access to the drug,” and “to the extent practicable,” that ETASU be structured “so as to minimize their burden on the health care delivery system.”<sup>15</sup> FDA believed that the restriction to a single pharmacy was not necessary or appropriate to ensure the safe use of Xyrem, and that any pharmacy that could meet the requirements for certification could safely dispense Xyrem. FDA was also concerned that the restriction to a single pharmacy in the REMS could unduly burden patient access and the health care delivery system.<sup>16</sup>

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<sup>10</sup> Jazz REMS proposal, August 24, 2009.

<sup>11</sup> Id.

<sup>12</sup> See Complete Response Letter for NDA 022531, October 8, 2010.

<sup>13</sup> FDA Interim Comments on proposed REMS, August 31, 2012.

<sup>14</sup> FD&C Act Section 505-1(f)(1)

<sup>15</sup> FD&C Act Section 505-1(f)(2)(A), (C), and (D).

<sup>16</sup> Dispute Appeal Denied Letter, February 27, 2015.

In its 2013 SEC filings, Jazz noted that it expected FDA modifications to the Xyrem REMS and stated that, “depending on the extent to which certain provisions of our Xyrem deemed REMS which are currently protected by our method of use patents covering the distribution of Xyrem are changed as part of updating our REMS documents, the ability of our existing patents to protect our Xyrem distribution system from generic competitors may be reduced.”<sup>17</sup>

In December, 2013, in an effort to bring the protracted discussions over the Xyrem REMS to a close, FDA informed Jazz that the Agency was requiring a modification to the REMS under the Agency’s statutory authority<sup>18</sup> which, among other things, would remove the single pharmacy limitation. FDA also sent a draft template for the REMS to the ANDA (b) (4) to facilitate the development of an SSS for sodium oxybate.

On February 28, 2014, Jazz filed a formal dispute resolution request, appealing the Division of Neurology Product’s REMS modification notification and claiming that the Agency’s “assertion that the closed-loop distribution system for Xyrem is no longer necessary is not only unsupported, it puts patients and others at risk.”<sup>19</sup> Jazz also argued that FDA did not have authority to modify the Xyrem REMS.<sup>20</sup>

FDA (through the Office of New Drug Evaluation I) denied Jazz’s dispute resolution request on May 8, 2014,<sup>21</sup> and Jazz appealed this decision to the Director of the Office of New Drugs on June 23, 2014.<sup>22</sup> At a meeting with FDA to discuss the ongoing dispute, a Jazz representative acknowledged that it might be possible for a distribution system that involves two, and perhaps more, specialty pharmacies to effectively prevent the abuse, misuse, and diversion of sodium oxybate.<sup>23</sup> Also at this meeting, FDA expressed two primary public health goals: (1) to have a REMS that assures safe use of the drug, and (2) to ensure that the REMS does not stand in the way of generic approval.

In light of the significant drain on Agency resources posed by the dispute, and the fact that the outcome of Jazz’s challenge to the Agency’s legal authority to require a

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<sup>17</sup> Form 10-Q, September 30, 2013, at p.54.

<sup>18</sup> See section 505-1(g)(4)(B) of the FD&C Act, which authorizes FDA to require a modification to an approved REMS either to (1) ensure the benefits of the drug outweigh the risks of the drug; or (2) minimize the burden on the health care delivery system of complying with the strategy.

<sup>19</sup> Jazz Formal Dispute Resolution Request (FDRR), February 28, 2014.

<sup>20</sup> Jazz argued, among other things, that FDA lacked statutory authority to modify a REMS “deemed” to be in effect by operation of FDAAA, and alternatively, even if FDA did have such authority, it could only be exercised to add restrictions to a REMS, not to modify or remove elements. Jazz FDRR, February 28, 2014.

<sup>21</sup> Appeal Denied Letter to Jazz from Office of Drug Evaluation I, May 8, 2014.

<sup>22</sup> Appeal of Decision by the Office of Drug Evaluation I, June 23, 2014.

<sup>23</sup> Minutes from meeting on August 13, 2014.

modification to a “deemed REMS” had the potential to affect only a small number of drug products,<sup>24</sup> the Agency decided to approve the REMS Jazz had proposed (i.e., with the single, central pharmacy limitation), and deny the dispute as moot.<sup>25</sup> However, the letter from Dr. Jenkins, Director of the Office of New Drugs, denying Jazz’s appeal states the following:

Our action approving the REMS submitted by Jazz should not be construed or understood as agreement with Jazz that limiting dispensing to a single pharmacy is the only way to ensure that the benefits of Xyrem outweigh the risks under section 505-1 of the FD&C Act. We continue to be concerned that limiting the distribution of Xyrem to one pharmacy imposes burdens on patient access and the healthcare delivery system. No other currently approved REMS requires a sponsor to limit dispensing to a single pharmacy.

At this time, FDA finds that the REMS approved today meets the applicable statutory standards. FDA intends to evaluate the Xyrem REMS, including the burdens it imposes, on an ongoing basis and will require modifications as appropriate.

## 2. History of SSS Development Efforts

The first ANDA to reference Xyrem, submitted by Roxane, was received by FDA on July 8, 2010. Roxane first contacted Jazz regarding the development of an SSS REMS on October 12, 2012.<sup>26</sup> (b) (4)

On January 23, 2014, FDA hosted a meeting between Jazz and the ANDA (b) (4) to facilitate the development of an SSS REMS for sodium oxybate. At this meeting, the ANDA (b) (4) provided a proposed timeline to the meeting attendees with 30, 60, and 90 day milestones with deliverables. For example, the ANDA (b) (4) committed to providing Jazz a draft confidentiality and disclosure agreement (CDA)—typically a prerequisite to substantive discussions about the formation of an SSS—shortly after the meeting with the goal of having it fully executed within 30 days. FDA requested that the parties submit bi-weekly updates to the Agency on the status of negotiations.<sup>27</sup>

<sup>24</sup> At that time there were only three “deemed” REMS remaining, including Xyrem.

<sup>25</sup> Dispute Appeal Denied Letter to Jazz from Office of New Drugs, February 27, 2015.

<sup>26</sup> See ANDA 202090, Sequence 0013 (Mar. 20, 2013).

<sup>27</sup> Minutes of meeting, January 23, 2014. As noted below, the negotiations are described very differently by Jazz and the ANDA (b) (4) and both Jazz and the ANDA (b) (4) accuse the other of

The ANDA (b) (4) provided a draft CDA to Jazz on January 28, 2014. On February 14, 2014, Jazz provided a draft CDA that was substantially revised. Negotiations over the CDA ensued, and the agreement was not fully executed until the end of August 2014, more than seven months after the initial draft was shared.<sup>28</sup>

In March, 2014, the ANDA (b) (4) having learned of the dispute resolution request by Jazz, expressed concern that “any dispute resolution process will be a protracted matter which will further delay the implementation of a REMS.”<sup>29</sup> FDA responded by stating that all parties should continue working together to develop an SSS for sodium oxybate products.<sup>30</sup>

Over the Summer of 2015, communication between the parties showed a continued inability to agree on threshold issues in the negotiations for an SSS. For example, Jazz’s summary of a call between the parties on June 24, 2015, describes the parties’ disagreement on voting rights for the negotiations. It states:

Jazz’s proposal included provisions for consensus decision making during development of shared REMS, with voting decision making after development, after approval and after implementation changing in accordance with parties’ approval and/or market share status. ANDA (b) (4) proposal provides that all decision making will be determined by majority vote of parties who have NDA or ANDA (and who have paid any costs then due) regardless of such parties’ approval status or market share.<sup>31</sup>

On August 19, 2015, the ANDA (b) (4) emailed the Agency to report a “lack of progress with Jazz on key terms for an operating agreement.”<sup>32</sup> The ANDA (b) (4) indicated that, as a result of the lack of progress, they intended to develop a proposal for a separate REMS.

On October 13, 2015, FDA hosted a tele-conference with Jazz and the ANDA (b) (4) to jointly discuss the status of their efforts to develop an SSS REMS. The ANDA

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mischaracterizing events. See, e.g., September 9, 2015 email from M. Shumsky for Roxane; September 25, 2015 email from J. Gold for Jazz; December 28, 2016 letter from M. Shumsky for Roxane to K. Uhl, FDA; (b) (4)

See ANDA 202090, Sequence 0038 (Jan. 4, 2017).

<sup>29</sup> Email from Gregory Hicks to FDA, March 12, 2014.

<sup>30</sup> Email from FDA to Gregory Hicks, March 26, 2014.

<sup>31</sup> Email from Jana Gold, Jazz to ANDA (b) (4) dated July 20, 2015.

<sup>32</sup> (b) (4)

(b) (4) explained that the parties were at an impasse on several major threshold issues. The first was voting rights. The ANDA (b) (4) wanted a voting structure based on “one company-one vote” as was the structure in other SSS REMS in which they had participated, while Jazz wanted voting by consensus until after approval and implementation of the REMS. The second threshold issue related to the process for negotiating an SSS. Jazz maintained that the ANDA (b) (4) were stalling the negotiations by refusing to proceed with legal and operational discussions on a parallel track, which would require integration of operational personnel into the legal negotiations. The ANDA (b) (4) responded that the negotiations needed to be sequential rather than parallel, because the CDA they signed precluded the ANDA (b) (4) from using any of the information from the negotiations for an SSS REMS in the possible future development of a separate REMS for ANDA sponsors. Therefore, if their operations staff were involved in discussions regarding the legal agreement with Jazz for an SSS, those staff would be precluded from later working on a separate system. The ANDA (b) (4) stated that this put them in an untenable position, knowing that the SSS negotiations were by no means guaranteed to be successful, and essentially would have required the ANDA (b) (4) to forfeit their right to obtain a waiver if necessary.<sup>33</sup>

On December 4, 2015, Jazz submitted a letter to the Agency expressing its opposition to a potential waiver of the SSS requirement for sodium oxybate.<sup>34</sup> In it, Jazz argued, among other things, that FDA cannot grant a waiver and approve a separate REMS for generics that utilizes multiple pharmacies, instead of a single, central pharmacy. The agency has carefully considered Jazz’s arguments and rejected them for the reasons described in section III below.

FDA hosted another joint tele-conference with the parties on March 23, 2016, to determine whether any progress had been made on these threshold issues. The parties did not appear to be any further along in resolving these disagreements than they had been five months before.<sup>35</sup>

In April, 2016, the ANDA (b) (4) submitted a REMS amendment (b) (4) proposing a joint separate REMS system for generic sodium oxybate. On December 2, 2016, the ANDA (b) (4) submitted a subsequent REMS amendment. (b) (4), Roxane, (b) (4) submitted requests that FDA waive the SSS requirement dated

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<sup>33</sup> Minutes of t-con, October 13, 2015.

<sup>34</sup> Letter in opposition to potential waiver of the SSS requirement, December 4, 2015 (December 4 Submission).

<sup>35</sup> Minutes of t-con, March 23, 2016.

December 28, 2016.<sup>36</sup> (b) (4) Roxane) requested a waiver pursuant to both statutory grounds described in section 505-1(i)(1)(B) of the FD&C Act.

### III. Discussion

The Agency has determined that a waiver of the SSS requirement for sodium oxybate is appropriate because the burden of creating an SSS outweighs the benefit of a single system, taking into consideration the impact on health care providers, patients, the ANDA (b) (4) and the holder of the reference drug product.

Although an SSS for all sodium oxybate products, including Xyrem, would likely provide the greatest efficiencies for stakeholders once implemented, the burden of negotiating an SSS has been substantial. In the more than four years since the first ANDA applicant and Jazz first began negotiating an SSS REMS<sup>37</sup> they have been unable to develop one. In fact, during that time, the parties (b) (4) have reached an impasse on governance issues without even broaching the substantive issues involved in developing an SSS REMS.

The negotiations are described very differently by Jazz and by the ANDA (b) (4) and both Jazz and the ANDA (b) (4) accuse the other of mischaracterizing events.<sup>38</sup> For example, Jazz claims that ANDA (b) (4) are being “incentivized to hinder productive SSSR development by creating pretexts for waiver.”<sup>39</sup> The ANDA (b) (4) state that Jazz has engaged in a strategy that “entails serial attempts to impose unreasonable contractual terms and conditions on the ANDA (b) (4) while concurrently issuing self-serving statements to FDA and the ANDA (b) (4) about Jazz’s commitment to the process.”<sup>40</sup>

We recognize that there are financial incentives and considerations on both sides that can hinder (b) (4) efforts to establish an SSS REMS. Certain statements by Jazz, including the concerns expressed in its SEC filings and its change in position regarding the necessity of the single pharmacy requirement (from urging FDA to remove the

<sup>36</sup> See ANDA 202090, Sequence 0038 (Jan. 4, 2017); (b) (4)

<sup>37</sup> Roxane’s ANDA was received on July 8, 2010. FDA sent Roxane a REMS Notification Letter on September 27, 2012. Roxane first contacted Jazz regarding formation of an SSS REMS on October 12, 2012.

<sup>38</sup> See, e.g., September 9, 2015 email from M. Shumsky for Roxane and September 25, 2015 email from J. Gold for Jazz. We note that not only are the parties prospective competitors, but patent infringement litigation has been ongoing between Jazz and one or more of the ANDA sponsors during this time.

<sup>39</sup> December 4 Submission at p.4.

<sup>40</sup> ANDA (b) (4) response to FDA questions, October 8, 2014.

restriction to a single pharmacy in 2009 to insisting it is critical to safe use in 2011), suggest Jazz's awareness that the Xyrem REMS could have the effect of blocking or delaying approval of generic versions of Xyrem.

Regardless of whose characterization of events is more accurate, the parties have been attempting to negotiate an SSS REMS for sodium oxybate for a substantially longer period of time than the applicants for alosetron or buprenorphine, the other drug products for which an SSS waiver has been granted.<sup>41</sup> Further, there is little FDA can do to force the two sides to agree to particular terms, because although the FD&C Act mandates that the RLD holder and the generic applicant use an SSS REMS, the Agency has no effective enforcement mechanism to compel the parties to participate in an SSS REMS, or to do so on specific terms. The enforcement mechanisms under the FD&C Act generally are designed to further FDA's public health mission,<sup>42</sup> not to mediate or resolve corporate disputes over governance issues or address behavior that one or more parties claim is anticompetitive.<sup>43</sup>

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<sup>41</sup> The first waiver of the SSS requirement was issued to the ANDAs referencing Subutex (buprenorphine) or Suboxone (buprenorphine and naloxone). In that case, the ANDA products were approved with a waiver of the SSS requirement approximately one year after SSS negotiations began (see Memorandum re: decision to waive the requirement for a single, shared system REMS for buprenorphine-containing transmucosal products (submitted to ANDA 090819, et al., February 22, 2013)). The waiver of the SSS requirement for the ANDAs referencing Lotronex (alosetron) was the second and most recent occasion on which the Agency has waived the SSS REMS requirement. In that case, the waiver of the SSS requirement was granted and ANDA products were approved approximately three years after SSS negotiations began (see Memorandum re: decision to waive the requirement for a single, shared system REMS for alosetron products (submitted to ANDA 200652 on May 4, 2015)).

<sup>42</sup> The enforcement tools available to FDA under the REMS provisions include finding the drug is misbranded (§ 502) (21 U.S.C. § 352(y)), seizure of a product deemed to be misbranded (§ 304(a)) (21 U.S.C. § 334(a)), withdrawal of approval of the product due to safety and efficacy concerns (§ 505(e)) (21 U.S.C. § 355(e)), seeking to enjoin violative behavior (e.g., enjoining distribution of a misbranded or unapproved product (§ 302) (21 U.S.C. § 332), prohibiting the introduction or delivery for introduction into interstate commerce of the product (§ 505(p)) (21 U.S.C. § 355(p)), and imposing civil money penalties (§ 303) (21 U.S.C. § 333(f)(4)).

<sup>43</sup> Jazz has requested that FDA refer the parties to mediation under the Administrative Dispute Resolution Act of 1996 (ADRA) to resolve their disagreement over business issues regarding the governance of any SSS REMS. FDA has declined to do so, both because the ADRA does not appear to apply by its terms and because the Agency has determined that it would not be an efficient use of limited government resources. Jazz's letter states that the ADRA gives FDA authority to refer the ongoing negotiations to mediation or another form of alternative dispute resolution as a way of resolving the parties' business issues, and that the ADRA is applicable to facilitating negotiations between parties, because it defines an "issue in controversy" as an "issue which is material to a decision concerning an administrative program of an agency, and with which there is disagreement... (B) between persons who would be substantially affected by the decision" (5 U.S.C. § 571(8)(B)). While it may be true that an "issue in controversy" can apply to two parties external to the Agency, we disagree that the business issues here are "material to a decision concerning an administrative program" of the Agency. Rather, the governance issues on which the parties disagree have little or no bearing on whether FDA can ultimately find that the standard for waiving the SSS requirement is met or whether an ANDA for sodium oxybate meets the statutory standard for approval. Moreover, under the ADRA, an "administrative program" is a federal function that involves protection of

In the absence of a waiver of the SSS requirement, the ANDA (b) (4) and Jazz's failure to agree to SSS terms is likely to further delay the approval of a generic version of sodium oxybate. Given the extensive negotiations that have occurred, the inability of the parties to agree to terms, and the Agency's lack of an effective mechanism to require them to do so, FDA concludes that, similar to the two previous instances where FDA granted a waiver of the SSS requirement, the burden of creating an SSS REMS in this instance appears to be insurmountably large.

#### **A. The Burden of Creating a Single, Shared System Outweighs the Benefits**

In accordance with section 505-1(i)(1)(B) of the FD&C Act, the Agency has considered the impacts that granting a waiver and permitting a second, separate REMS for sodium oxybate will have on health care providers, patients, the ANDA (b) (4) and the reference drug sponsor (Jazz). The Agency concludes that, on balance, the impacts on these stakeholders favor granting a waiver. While an SSS would provide benefits to stakeholders by avoiding the potential confusion and inefficiency associated with the co-existence of two REMS for sodium oxybate, these benefits do not outweigh the burdens of (1) the time and resources expended by the parties to create an SSS REMS, and (2) a

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the public interest and the "determination of rights, privileges, and obligations of private persons through rule making, adjudication, licensing, or investigation" (Section 571(2)). The current negotiations for an SSS REMS for sodium oxybate do not appear to fit this description. They are negotiations between private parties regarding their business relationship, to which FDA is not a party. The FDA is not engaged in any rulemaking, adjudication, licensing, or investigation with respect to the governance of a shared system REMS. While FDA may facilitate communication and negotiation between the parties, we are not determining any rights, privileges or obligations in doing so. Moreover, FDA is not aware of any circumstances in which the Agency has utilized the provisions of the ADRA, or any other statutory provisions, to refer private parties to mediation and Jazz has provided no such examples. Jazz refers in its letter to the Department of Health and Human Services (HHS) Alternative Dispute Resolution Division program. However, this program provides alternative dispute resolution services in appeals filed with the Departmental Appeals Board's other three Divisions (Appellate, Civil Remedies and Medicare Operations Division) and is therefore inapplicable.

Jazz cited two examples where FDA purportedly "has established dispute resolution under the ADRA" by referring to guidance documents from the Center for Veterinary Medicine and the Center for Devices and Radiological Health. The guidance documents to which it refers apply to veterinary drugs and medical devices, and are not binding on FDA or the public. Each of these guidance documents explicitly applies to dispute resolution for "scientific controversies" between the Agency and a regulated party. Both were issued to aid in implementation of the dispute resolution provision in the Food and Drug Administration Modernization Act of 1997 (FDAMA), which was designed to ensure that FDA makes appropriate use of independent scientific experts to advise the agency on "scientific controversies" between FDA and a sponsor, applicant, or manufacturer (Section 562 of the FDCA). The current disagreement between Jazz and the ANDA (b) (4) regarding governance of an SSS REMS for sodium oxybate is neither a scientific controversy nor a disagreement between the Agency and a regulated party. Accordingly, we do not find these examples to be relevant.

Even assuming that the ADRA applies, its application is discretionary. It is our view that invoking the ADRA to refer the parties to mediation regarding business issues that--however they are decided--ultimately are not relevant to the statutory standard for approving a REMS, is not an efficient use of limited governmental resources. We note that the parties were not prevented from pursuing mediation on their own.

delay in the approval of one or more equally safe generic sodium oxybate alternatives. The Agency's findings with respect to the impacts on each stakeholder group of having two REMS are summarized below.

### **1. Health Care Providers**

The creation of two REMS will create some inefficiencies for prescribers and pharmacies/pharmacists. Specifically, health care providers who wish to have the ability to prescribe Xyrem as well as a generic sodium oxybate product will have to enroll in two REMS programs. That means that a prescriber must complete and submit a separate prescriber enrollment form to the ANDA REMS. That step need only be completed once, however, and the form is short—just one page. Further, the prescribing information and prescriber brochure a prescriber must review as part of enrollment are nearly identical to the Xyrem labeling and prescriber brochure, and the required attestations (e.g., prescriber agreement to provide certain counseling, screening, and monitoring for each patient) on the enrollment form are the same.

Once enrolled in the ANDA REMS, the burden on a prescriber in operating under the REMS is the same as under the Xyrem REMS: he or she must enroll, assess, and counsel each patient, and submit a prescription form to the certified pharmacy. Again, both forms are just one page each and nearly identical to the Xyrem REMS materials. The prescriber is also required to reassess the patient within the first 3 months of starting sodium oxybate therapy, and it is recommended every 3 months thereafter. The prescriber is required to report adverse events, including any cases of suspected abuse, misuse, or diversion, to *either* the Xyrem or the ANDA REMS, as appropriate, but need not report to both. As such, the creation of two REMS should not impose an additional burden with respect to enrollment, counseling, assessment, or adverse event reporting.

A pharmacy that wishes to dispense generic sodium oxybate will need to have their pharmacists and other staff complete a training program similar to the Xyrem REMS pharmacy training program and complete a short form to become certified in the ANDA REMS. This step need only be completed once. Because the Xyrem REMS currently specifies use of only a single pharmacy, any pharmacy other than the Xyrem pharmacy would be enrolling only in the sodium oxybate REMS program. Therefore, any pharmacy dispensing sodium oxybate would need to take only one training program.

Certain communication between pharmacies will also be needed. First, a pharmacy certified in the ANDA REMS must, for each prescription received, contact the Xyrem REMS to request verification that: (1) the patient has no active overlapping prescription(s) for Xyrem; and (2) the patient and prescriber have not been disenrolled for suspected abuse, misuse, or diversion. Second, the ANDA REMS program also must report to the Xyrem REMS pharmacy on an ongoing basis each prescription filled and

any instances of patient/prescriber disenrollment in the ANDA REMS program. These communications will be documented.

The Xyrem REMS pharmacy will receive these reports from pharmacies certified in the ANDA REMS program and enter all relevant safety information into the Xyrem central database, as it is required to do under its REMS.<sup>44</sup>

The reporting of prescription fills and disenrollment will be only a minimal additional burden on the pharmacies in both programs. We do not expect the overall number of patients or the total number of prescriptions dispensed to change substantially as a result of the approval of generic products. The difference will be that some of the prescriptions currently being filled by the Xyrem pharmacy likely will instead be filled by pharmacies certified under the ANDA REMS program. Therefore, some of the time the Xyrem REMS pharmacy previously spent on filling prescriptions for Xyrem presumably will now be spent receiving information from the ANDA REMS program pharmacies and entering it into the Xyrem REMS database. Although this shift likely will result in a reallocation of resources, we do not expect that it will result in an overall increased burden on the Xyrem pharmacy. Accordingly, FDA does not believe that the waiver of the SSS requirement will impose a significant burden on health care providers.

## **2. Patients**

The Agency finds that, while a waiver will result in some burdens on patients due to the existence of two programs, these burdens will be minimal. As discussed further in section III(C) below, the Agency finds that the proposed sodium oxybate REMS will afford patients the same level of safety as the Xyrem REMS.

While two REMS will mean that some patients<sup>45</sup> may need to enroll in two REMS programs, the burden associated with enrollment (completing a form during a physician visit and receiving counseling) is a modest, one-time obligation. Moreover, the REMS materials required in both programs will contain the same safety messages about sodium

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<sup>44</sup> See, e.g., Xyrem REMS section II(B)(2)(a)(iv) (to become certified in the REMS program, the pharmacy must agree to “Utilize the secure and validated XYREM REMS Program Central Database,”; section II(B)(2)(d)(i) (the certified pharmacy “will document these events, including all requests for early refills, in the XYREM REMS Program Central Database by completing an RMR [Risk Management Report],”); and II(C)(1)(c) (“The XYREM REMS Program Central Database will contain patient and prescriber enrollment status, all completed data forms, prescription and shipment data, as well as information related to dosing, concomitant medications, and behavior that raises suspicion of abuse, misuse, or diversion, including complete Risk Management Report histories.”).

<sup>45</sup> The Agency anticipates that most patients will use either generic sodium oxybate or Xyrem, but not both. Existing patients wishing to use generic sodium oxybate will need to enroll in the new ANDA REMS program. New patients presumably would enroll in either the ANDA REMS program or the Xyrem REMS program, but not both. The Agency expects that only a very small number of patients would need to be enrolled in both REMS programs at the same time.

oxybate. As a result, FDA does not believe that the co-existence of the two REMS will be a significant burden to patients or compromise the clarity of the safety messages communicated to them.

Jazz has raised the concern that patients switching between the Xyrem REMS and the ANDA REMS, which uses different databases, would mean loss of access to the patient's prior sodium oxybate history, negatively impacting patient care and security.<sup>46</sup> The Agency does not agree.

If patients do switch between the REMS programs, the patient history data that are relevant to identifying any abuse, misuse, or diversion will not be lost. The ANDA REMS requires its certified pharmacies to contact the Xyrem central pharmacy to verify that a patient has not been disenrolled from the Xyrem REMS and identify any overlapping prescriptions prior to dispensing. The ANDA REMS further requires its certified pharmacies to communicate the patient's corresponding prescription information to the Xyrem central pharmacy. The Xyrem central pharmacy is required to enter all relevant safety information into its central database to use for prescription verifications.<sup>47</sup> This pharmacy-to-pharmacy communication will ensure that each REMS program can access a patient's relevant sodium oxybate history.<sup>48</sup>

The inability of the ANDA (b) (4) and Jazz to create an SSS imposes a significant burden on patients in that it bars access to one or more equally safe generic sodium oxybate products. FDA has been waiting to approve any sodium oxybate ANDAs pending development of an SSS REMS.<sup>49</sup>

Jazz has argued that patient access does not hinge on, and would not be realized by, a decision to waive the SSS requirement for sodium oxybate, because comprehensive resolution of intellectual property litigation between Jazz and ANDA (b) (4) is not likely to occur for some time.<sup>50</sup> Given the ongoing litigation, Jazz states that patient access to generic sodium oxybate could conceivably be realized more quickly through

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<sup>46</sup> December 4 Submission at 31.

<sup>47</sup> See fn. 44 supra.

<sup>48</sup> Both the Xyrem REMS and the ANDA REMS require that documentation of instances of potential abuse, misuse, or diversion be maintained in their respective databases and reviewed prior to dispensing (Xyrem REMS section II(B)(2)(b)(iii)(b); ANDA REMS section II(B)(2)(b)(ii)(2)(b)). The Agency considered whether additional reporting between the programs would be appropriate, such as reporting of all Risk Management Reports (RMRs) generated, and concluded such information would not be useful. Most RMRs do not report issues that indicate a patient should not receive the drug (e.g., early refill request due to a prescribed dose increase), and those that do would lead to disenrollment, which is required to be communicated between the REMS programs. FDA concluded that the reporting of every RMR between the programs would potentially burden both systems without improving safety.

<sup>49</sup> Delay may also impose a substantial cost to the U.S. healthcare system, as Xyrem remained, until now, shielded from generic competition.

<sup>50</sup> December 4 Submission at 32.

continued negotiation for an SSS rather than a waiver of the SSS requirement.<sup>51</sup> FDA is not privy to the details of the litigation and cannot comment on the merits. However, as explained above, after four years of unsuccessful negotiation for an SSS it seems unlikely that continued discussions will yield results in the near term. Thus, even if the burden on patients of the lack of access to potentially more affordable sodium oxybate alternative is not immediately ameliorated by the granting of a waiver, that burden will be removed once the first generic product comes to market. Moreover, by issuing a waiver and approving an ANDA, FDA is taking one critical and fundamental step to alleviate that burden on patients.

In short, the burden of creating an SSS here denies patients access to one or more potentially more affordable sodium oxybate alternatives, while the potential benefit of an SSS is that some patients will not have to enroll in two REMS programs and receive the duplicative educational materials associated with having two REMS programs.

### 3. ANDA (b) (4)

Absent a waiver, approval of pending ANDAs will be delayed until the parties reach an agreement on an SSS REMS. There are obvious incentives for any innovator company, including Jazz, to delay generic competition, including by failing to agree on SSS REMS terms. Jazz asserts that it is the ANDA (b) (4) hindering SSS development and seeking a waiver in order to avoid the time, money, and effort associated with development of an SSS.<sup>52</sup> This argument assumes that the expenditure of time, money, and effort would be less significant to develop a separate REMS system. The Agency notes, however, that the ANDA REMS is a shared system (b) (4), and therefore required its own time, money, and effort to develop. Given that these factors did not prevent the ANDA (b) (4),<sup>53</sup> it does not appear that an unwillingness to invest the time, money, and effort to develop a shared program is the underlying barrier to development of an SSS in this case.

By granting a waiver, the Agency will remove a barrier to generic products coming to market. The Agency's decision to grant a waiver will benefit the ANDA (b) (4) to the extent it will allow ANDA applications that otherwise meet the statutory standard to be approved, the result intended by the Hatch-Waxman amendments. The burden of SSS development outweighs any potential benefit to ANDA applicants from such a system.

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<sup>51</sup> Id.; see also, Letter from Jazz to FDA, December 5, 2016.

<sup>52</sup> Id. at 29.

<sup>53</sup> The ANDA (b) (4) began negotiations for a separate REMS in October, 2014 (see ANDA (b) (4) response to FDA questions, October 8, 2014) and (b) (4) began contracting third party vendors to build the system in August, 2015 (see (b) (4)).

#### 4. Jazz

Jazz argues that a waiver will affect its ability to continue using its approved REMS and impact patient safety because “without access to all of the data, Jazz would lose the ability to ensure that the pharmacy has all of the data necessary to monitor for overlapping prescriptions, review for potentially interacting agents that are unknown to the prescriber, and review of alerts and RMRs regarding potential misuse, abuse, or diversion...”<sup>54</sup> However, Jazz will continue to have access to the data it needs to fulfill all of the safe use requirements in its approved REMS. As explained in sections III(A)(1) above and III(C) below, the ANDA REMS requires pharmacies certified in that REMS to report to the Xyrem REMS each prescription filled as well as each instance of patient/prescriber disenrollment in the ANDA REMS. This will provide the Xyrem pharmacy the data necessary to monitor for overlapping prescriptions and disenrollments for potential misuse, abuse, or diversion. Jazz will not lose data necessary to monitor potentially interacting agents unknown to prescribers, because each REMS program requires their certified pharmacies to screen for concomitant medications and document them in their respective database(s).<sup>55</sup> The Xyrem program will not need to check the ANDA program databases for this information, because the Xyrem pharmacy will obtain that information independently from enrolled prescribers and patients and will add that information to its own database. Therefore, Jazz will continue to have access to the data it needs to fulfill all of the safe use requirements in its approved REMS.

Jazz also argues that any negative outcomes of a separate REMS for sodium oxybate ANDAs (i.e., increased risk associated with distribution) would put Jazz at risk for increased liability. As explained below, FDA has carefully reviewed and considered the ANDA (b) (4) proposed REMS program and has determined that it describes a secure and cohesive system and does not create an increased risk of abuse, misuse, or diversion. Because FDA finds that the ANDA (b) (4) proposed REMS program would assure the same level of safety as the existing Xyrem REMS program, FDA does not anticipate that Jazz will experience a meaningful increase in liability.

Approving sodium oxybate ANDAs would allow patients and the healthcare system access to alternative versions of the drug and increase competition in the marketplace.<sup>56</sup>

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<sup>54</sup> December 4 submission at 33.

<sup>55</sup> Xyrem REMS document Section II(B)(2)(b)(i); ANDA REMS document Section II(B)(2)(b)(i).

<sup>56</sup> In a letter to FDA dated December 5, 2016, Jazz requested that it be informed of any effort by the ANDA (b) (4) to form a separate REMS and that Jazz have the opportunity to review and evaluate the ANDA REMS prior to approval. FDA denied a similar request made by Prometheus Laboratories, Inc. in a 2013 citizen petition (Docket No. FDA-2013-P-0572) regarding the REMS for Lotronex (alosetron), and declines to do so here as well. As explained in that petition response, FDA welcomes input from RLD sponsors at any point on whether a waiver of the SSS requirement should be granted. In this case, FDA has considered such information submitted by Jazz as described in this memorandum.

The benefit of an SSS is the potential for reducing the burden on stakeholders of having separate REMS programs. However, as described above, those burdens in this case are minimal and the potential benefit of alleviating them is far outweighed by the significant burden of continued SSS negotiations and of denying patients access to generic versions of the drug for an indefinite period of time.

**B. (b) (4) ANDA (b) (4) unable to obtain a license for the aspect of the ETASU claimed by Jazz in an unexpired patent and as a trade secret entitled to protection**

In accordance with Section 505-1(i)(1)(B)(ii), (b) (4), and Roxane (b) (4) certified that “an aspect of the elements to assure safe use for the applicable listed drug is claimed by a patent that has not expired or is a method or process that, as a trade secret, is entitled to protection, and the [ANDA (b) (4)] sought a license for use of an aspect of the elements to assure safe use for the applicable listed drug and (b) (4) unable to obtain a license.” This certification was made in waiver request (b) (4) to FDA dated December 28, 2016, from (b) (4) Roxane.<sup>57</sup>

Consistent with the statutory requirement that such a certification include “a description of the efforts made by the [ANDA] applicant to obtain a license,” Roxane’s letter states that the company proposed license terms to Jazz between October 2012 and September 2013. The letter states that Jazz refused those terms and declined to offer a substantive counterproposal. Additional discussions took place in 2016, but Roxane states that those were again unsuccessful. (b) (4)

(b) (4)

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<sup>57</sup> December 28, 2016 waiver request letter from M. Shumsky for Roxane to K. Uhl, FDA (ANDA 202090, Sequence 0038 (Jan. 4, 2017)); (b) (4)

(b) (4)

In December 2015, Jazz acknowledged that (b) (4) ANDA (b) (4) had “requested licenses to some of Jazz’s REMS patents” but stated that “(b) (4) certify that it has made reasonable efforts to obtain a license to Xyrem’s intellectual property.”<sup>59</sup> However, Jazz also indicated that it would be willing to discuss license terms only “once the contours of the shared REMS come into focus” and “*only* in the context of resolution of the [ongoing patent infringement] litigation, through settlement or otherwise.”<sup>60</sup>

As with the shared REMS negotiations, the patent license negotiations seem to be described differently by Jazz and the ANDA (b) (4). It would be difficult for FDA to assess the merits of these respective positions, but the statute does not require us to do so.<sup>61</sup> Under section 505-1(i)(B)(ii) of the FD&C Act, the Agency may waive the SSS requirement if: (1) an aspect of the ETASU for the applicable listed drug is claimed by a patent that has not expired; and (2) an ANDA applicant certifies that it has sought a license for use of an aspect of the ETASU and that it was unable to obtain a license. Both criteria are satisfied here.<sup>62</sup>

### **C. The ANDA (b) (4) proposed REMS is comparable to the approved REMS for Xyrem**

Section 505-1(i)(1)(B) of the FD&C Act provides that an ANDA is subject to the ETASU for the RLD, but a separate REMS for ANDA applicants that is waived from the SSS requirement can use a “different, comparable aspect of the [ETASU].” FDA interprets this standard to mean that a waived system for ETASU must include the same general elements as described in the statute. For example, if the RLD’s ETASU consist of prescriber certification (under 505-1(f)(3)(A)) and dispensing of a drug only in certain

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<sup>58</sup> Id.

<sup>59</sup> Jazz December 4, 2015 Submission at 35.

<sup>60</sup> Id. (emphasis added).

<sup>61</sup> Jazz argues that “the statute plainly gives FDA a role to play when it comes to issues concerning [REMS patent] licensing” because it authorizes the Agency to seek to negotiate a voluntary agreement with the patent owner if it receives a certification under 505-1(i)(B)(ii). Id. at 36. We agree that the statute provides the Agency with that authority, but disagree with the implication that such authority obligates FDA to second-guess the certifications made by ANDA applicants or to otherwise play a more prominent role in patent license negotiations. The authority to negotiate a voluntary agreement with the patent owner is discretionary, and given the longstanding disagreement between the parties over the SSS REMS and related patent issues, FDA declines to invoke this discretionary authority here.

<sup>62</sup> Jazz further argues that even if this waiver criterion were met, it would be “inappropriate” for FDA to grant a waiver because doing so would “eliminat[e] key safety measures that are essential to ensuring that sodium oxybate can be safely distributed.” Id. at 36-39. FDA disagrees with that conclusion for the reasons described in this memorandum.

healthcare settings (under 505-1(f)(3)(C)), the ANDA system must include those elements as well. FDA further interprets “different, comparable aspect of the [ETASU]” to allow a separate REMS for ANDA applicants to use different methods or operational means to effectuate a REMS requirement, provided the program achieves the same level of safety.

The ANDA <sup>(b)(4)</sup> proposed REMS has the same ETASU as those in the Xyrem REMS. The proposed ANDA REMS operationalizes these elements differently, and FDA has determined that those aspects of the ETASU are comparable to the Xyrem REMS. Specifically, both the Xyrem REMS and the ANDA REMS require that: (1) healthcare providers who prescribe the drug are specially certified<sup>63</sup>; (2) the drug will be dispensed only by pharmacies that are specially certified<sup>64</sup>; and (3) the drug will be dispensed and shipped only to patients who are enrolled in the REMS program with documentation of safe use conditions.<sup>65</sup> The following specific REMS requirements are the same:

1. **Prescriber Certification.** Both REMS require healthcare providers who prescribe sodium oxybate agree to perform the same functions, including patient screening, counseling, evaluating, enrolling, and reporting adverse events.
2. **Pharmacy Certification.** Both REMS require that the drug will not be stocked in retail pharmacies, and both require that their certified pharmacies<sup>66</sup> perform the same functions:
  - a. Dispense only to patients that are enrolled in the REMS
  - b. Ensure that all pharmacy staff involved in the program are trained
  - c. Ensure that pharmacists involved in the program are trained
  - d. Utilize database(s) for tracking and documenting the relevant prescription and enrollment information
  - e. Provide toll-free access to a REMS program pharmacist
  - f. Ship the drug directly to each patient or designee and track the shipment
  - g. Limit the first shipment to a one-month supply and subsequent shipments to no more than a three-month supply
  - h. Document and report all potential adverse events to the sponsor(s)
  - i. Ensure completion of patient counseling checklist and its requirements and the documentation of information received

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<sup>63</sup> See section 505-1(f)(3)(A) of the FD&C Act.

<sup>64</sup> See section 505-1(f)(3)(B) of the FD&C Act.

<sup>65</sup> See section 505-1(f)(3)(D) of the FD&C Act.

<sup>66</sup> The Xyrem REMS specifies use of the single pharmacy, while the ANDA REMS contemplates multiple certified pharmacies.

- j. Validate each prescription by
    - i. verifying that both prescriber and patient are enrolled and that the patient has no other active prescription
    - ii. confirming all prescription information
  - k. Review the patient information, including concomitant or interacting agents, and reports regarding potential abuse, misuse, or diversion
  - l. Monitor, document, and report to sponsor(s) all instances of patient or prescriber behavior that give rise to a reasonable suspicion of abuse, misuse, or diversion.
3. **Documentation of Safe Use Conditions.** Both REMS require that the drug only be shipped to patients who are enrolled in the REMS program with documentation of the same safe use conditions:
- a. The drug is dispensed only by a certified pharmacy, by direct shipment, to patients enrolled in the program
  - b. Patients are enrolled in the program only if a prescriber completes the patient enrollment form
  - c. The drug is dispensed and shipped only to patients who have signed the prescriber-completed patient enrollment form and acknowledged that he/she has been counseled and asked any questions
  - d. Patients remain in the program unless the pharmacy or prescriber determine they should be disenrolled
  - e. Disenrolled patients may re-enroll under certain conditions
  - f. Patients may change prescribers provided that the new prescriber is also enrolled in the program and that the new prescription does not overlap with another active prescription.

The ANDA REMS requires that sodium oxybate can be prescribed only by certified prescribers, and dispensed only to enrolled patients by certified pharmacies.<sup>67</sup> Only a mail order pharmacy that coordinates secure shipment to patients and is not open to the public can be certified to dispense sodium oxybate. The ANDA REMS also contains the same statement as the Xyrem REMS that sodium oxybate “will not be stocked in retail pharmacy outlets.”<sup>68</sup>

There are some differences in the operational aspects of the ETASU. Specifically, the ANDA REMS does not include the same limitations on the number of pharmacies and databases used. While the Xyrem REMS uses a single pharmacy and a single database,

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<sup>67</sup> The Xyrem REMS states that “Xyrem will be dispensed only by the central pharmacy that is specially certified.”

<sup>68</sup> ANDA REMS section II(B)(2)(a) and II(C)(1)(b).

the ANDA REMS will use multiple certified pharmacies and multiple databases connected via an electronic communication verification mechanism known as a switch system. The switch system ensures coordination among prescribers and pharmacies such that a drug is dispensed only after there is verification that all safe use conditions are met, namely that: (1) the patient is enrolled in the REMS, meaning that, among other things, the patient has been screened by a trained prescriber and educated about the safe use of sodium oxybate; (2) the prescriber is certified in the REMS, meaning that, among other things, the prescriber has reviewed the prescribing information regarding the safe use of sodium oxybate and agreed to report adverse events promptly; and (3) a pharmacy trained about the particular risks of sodium oxybate and the REMS program requirements has validated the prescription and provided the required patient counseling.

A switch system has been used to verify safe use conditions in other approved REMS,<sup>69</sup> including the REMS for Transmucosal Immediate Release Fentanyl (TIRF) products.<sup>70</sup> TIRF products are Schedule II controlled substances that are contraindicated in non-opioid tolerant patients (among others) due to the risk of fatal respiratory depression, and pose risks of misuse, abuse, addiction, overdose, and serious complications due to medication errors. The switch system technology used in the TIRF REMS has been successfully implemented to verify, prior to dispensing, that the pharmacy and prescriber are enrolled and active and the patient has not been deactivated from the program.<sup>71</sup> The switch system provides this information to pharmacists at the point-of-dispensing, and if one or more of the required enrollments cannot be verified, then the switch system will reject the prescription, and the pharmacy will receive a rejection notice.

The ANDA REMS will use a switch system similar to the TIRF REMS to perform the necessary safety checks at the point of dispensing. Once a certified pharmacy receives the prescription, it requests a pre-dispense authorization (PDA) from the ANDA REMS via the switch system, which queries databases of patients, prescribers, dis-enrolled prescribers, and pharmacies, to verify the necessary prescription information and patient and prescriber enrollments before authorizing dispensing.

In addition to verifying this necessary safety information from its own databases, the ANDA REMS will require a certified pharmacy to contact the Xyrem REMS program to verify, prior to dispensing, that the patient has no other active prescriptions for Xyrem that overlap with the prescription to be filled, and to identify any patient and prescriber

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<sup>69</sup> The REMS for Addyi, Qsymia, and clozapine, among others, also utilize a switch system. See FDA REMS website at <http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm>.

<sup>70</sup> TIRF REMS document is available at <http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=60>.

<sup>71</sup> See e.g., TIRF REMS assessment review, September 28, 2016, at p.29.

dis-enrollments. A certified pharmacy in the ANDA REMS also will provide corresponding information (prescription information and enrollment status) to the Xyrem REMS program, so that the Xyrem pharmacy can include that information in its central database and verify prescriptions and enrollment status against the ANDA system.<sup>72</sup>

Once all checks are completed, the medication is shipped directly to the patient just as it is under the RLD program. The drug product is never housed in a retail pharmacy.

FDA has concluded that this approach achieves the same level of safety as the RLD. We have determined that the different aspects of the ETASU in the REMS proposed by the ANDA (b) (4) are comparable to those in the Xyrem REMS. In each case, the drug is shipped directly to the patient and not stocked on retail pharmacy shelves, the same patient counseling takes place prior to dispensing, and multiple checks are built in to ensure that safe use conditions have been met and that there have been no attempts at diversion, abuse or misuse. Accordingly, this conclusion is consistent with the Agency's stated position (described above) that limiting dispensing to a single pharmacy is not the only way to meet the necessary requirements for pharmacy certification and ensure that the benefits of Xyrem outweigh the risks.

#### *Controls under the ANDA REMS*

In its submission to the Agency dated December 4, 2015, Jazz states its opposition to a waiver of the SSS REMS requirement for generic sodium oxybate products. This submission predates the submission of the ANDA (b) (4) REMS, but Jazz refers to the ANDA (b) (4) "Paragraph IV notices"<sup>73</sup> as evidence that (b) (4) intend to deviate significantly from the approved Xyrem REMS.<sup>74</sup> Jazz describe ANDA (b) (4) stated intent to use "multiple separate sodium oxybate databases and multiple additional points of distribution" and quotes from the (b) (4) ANDA (b) (4) Paragraph IV notices to characterize the use of multiple databases as disconnected and incomplete.<sup>75</sup>

Jazz's description of the ANDA (b) (4) system does not accurately characterize the REMS being approved. The ANDA REMS does not permit the use of retail pharmacies, which Jazz maintains would entail shipment to, and stocking of sodium oxybate at,

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<sup>72</sup> The Xyrem REMS requires that the certified pharmacy access the REMS program database to verify all enrollments and prescription information prior to each dispense of the drug. See Section II(B)(2)(b)(ii).

<sup>73</sup> Pursuant to section 505(j)(2)(B) of the FD&C Act, an ANDA applicant that makes a certification described in subparagraph (A)(vii)(IV) shall give notice to certain recipients in accordance with this section. Such a "Paragraph IV notice" shall include a detailed statement of the factual and legal basis of the applicant's opinion that Jazz's REMS patents will not be infringed. See section 505(j)(2)(B)(iv)(II) of the FD&C Act.

<sup>74</sup> Dec.4 Submission at 9.

<sup>75</sup> Id. at 10.

additional sites upstream in the pharmaceutical distribution chain. On the contrary, the ANDA REMS requires that sodium oxybate only be distributed by wholesalers/distributors that are certified in the REMS, and that they distribute the drug only to certified pharmacies. As a result, sodium oxybate cannot be distributed to secondary wholesalers, which Jazz describes as “the weakest point in the U.S. pharmaceutical distribution chain.”<sup>76</sup> In other words, the ANDA REMS maintains strict controls on distribution and physical security of sodium oxybate.

While it is true that the ANDA REMS will use multiple pharmacies and multiple databases, these pharmacies and databases are connected in a way that accomplishes the same result as the Xyrem REMS. FDA therefore does not share Jazz’s view that the ANDA REMS significantly deviates from the approved Xyrem REMS. The differences between the programs do not reflect different ETASU, but rather are aspects of the ETASU that are being operationalized differently. Based upon the Agency’s expertise and experience with the use of switch technology in other REMS programs, we expect that the ANDA REMS for sodium oxybate will provide the same level of safety as the Xyrem REMS. Therefore, FDA has determined that these operational differences are comparable within the meaning of section 505-1(i)(1)(B) of the FD&C Act.

#### *Use of databases*

Jazz states that “the central database is necessarily one of the elements to assure safe use of Xyrem, because it is indispensable to the successful operation of the entire REMS.”<sup>77</sup> The Agency disagrees. From a safety perspective, the use of a central database is not “indispensable to the successful operation of the entire REMS.” As explained above, the ANDA REMS use of multiple databases connected by a switch system, together with required communications verifying and reporting key information between the ANDA REMS certified pharmacies and the Xyrem REMS certified pharmacy, assure a comprehensive review of the data necessary to ensure safe use of sodium oxybate. Consequently, FDA finds that the ANDA REMS program achieves the same level of safety as the Xyrem REMS central pharmacy’s use of a central database.

#### *Single pharmacy requirement*

We note that of the approved REMS that include pharmacy certification as an element, other than the Xyrem REMS, none requires use of a single pharmacy or even limits the pharmacies to a certain number. Though many companies *choose* to limit the number of pharmacies they utilize to implement their REMS, that is a business decision and not one

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<sup>76</sup> Id. at 24.

<sup>77</sup> Id. at 20.

required by the REMS. Rather, the REMS with pharmacy certification provisions specify the substantive criteria for certification that are necessary to assure safe use of the drug without stipulating how many pharmacies can or will be permitted to be certified.

To the extent that Jazz asserts a single central pharmacy is essential to safe use of the drug and no generic program can be safe without it, FDA notes that this was the primary disagreement between Jazz and the Agency in the dispute resolution over the finalized REMS for Xyrem, and the Agency has long maintained that use of a single central pharmacy is not the only way to safely distribute the drug.<sup>78</sup> FDA also notes the inconsistent position Jazz has taken on this subject and the statement Jazz made<sup>79</sup> suggesting knowledge that this aspect of its REMS could have the effect of preventing generic competition.

*“REMS regulatory science” and evidence of comparability*

Jazz further argues that FDA cannot grant a waiver of the SSS requirement because “[c]urrently available REMS regulatory science cannot provide evidence adequate to demonstrate comparability of differing aspects of sodium oxybate ANDA REMS to the Xyrem REMS.”<sup>80</sup> It goes on to state that “[t]he current state of evolution of REMS regulatory science has not developed the standards of evidence, tools, and methodology needed to reliably evaluate whether the level of risk mitigation associated with the existing Xyrem REMS will be maintained if one or more separate, waived REMS are introduced.”<sup>81</sup>

We disagree with Jazz’s view for two reasons. First, FDA’s conclusions regarding comparability here are based on experience with the successful use of switch systems to verify safe use conditions in other REMS; they are neither theoretical nor without support. Second, we find Jazz’s reading inconsistent with FDA’s statutory waiver authority. Under Jazz’s narrow reading, the Agency must develop “standards of evidence, tools, and methodology” to determine whether different aspects of the ETASU are comparable to the Xyrem REMS. The statute does not establish such requirements, and we decline to adopt them here. FDA has carefully reviewed the proposed REMS for the ANDA (b) (4) and has concluded that the differences in the way the ETASU are operationalized are comparable to the corresponding aspects of the ETASU in the Xyrem REMS.

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<sup>78</sup> See e.g., Meeting Minutes from August 14, 2013; dispute denial letter dated November 20, 2013.

<sup>79</sup> See fn. 17 supra.

<sup>80</sup> Dec. 4 Submission at p.25.

<sup>81</sup> Id. at p.26.

Consistent with other REMS, periodic assessments of both of these programs will allow the Agency to monitor compliance with each and make any modifications necessary to ensure the benefits of the drug continue to outweigh its risks. The assessment plan for the ANDA REMS requires the same metrics as the Xyrem REMS in order to determine that the REMS is meeting its goals. Assessments will be submitted to FDA at 6 and 12 months following approval and annually thereafter. The assessment plan will evaluate compliance with the sodium oxybate REMS Program requirements, including compliance with and evaluations of safe use procedures, corrective and preventative actions taken to address non-compliance with distribution and dispensing requirements, incidences of overlapping prescriptions, as well as early refill requests and any reports of behavior suspicious of abuse, misuse or diversion.<sup>82</sup>

#### **IV. A Conditional Waiver is Appropriate**

FDA is attaching the following condition to the waiver: the waiver-granted REMS shall be open to all current and future applicants with sodium oxybate products. The primary purpose of this condition is seek to minimize the number of ETASU systems with which patients, prescribers, and other stakeholders would need to comply.<sup>83</sup>

#### **V. Conclusion**

For the foregoing reasons, FDA has decided to waive the requirement that sodium oxybate products use an SSS REMS. The waiver is conditioned on a requirement that the ANDA (b) (4) make (b) (4) REMS open to all current and future applicants for sodium oxybate products. The Agency has also determined that the ANDA REMS contains the same ETASU as the Xyrem REMS and uses comparable aspects of those ETASU.

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<sup>82</sup> Details of the assessment plan will be included in the approval letter for any ANDA subject to the ANDA REMS.

<sup>83</sup> FDA has imposed the same condition in both other waivers of the SSS requirement: buprenorphine and alosetron.