DRAFT

MEMORANDUM

DATE: April 30, 2015

TO: Roxane's ANDA for alosetron hydrochloride tablets, 0.5 mg and 1 mg (ANDA 200652)

FROM: Dale Conner, Pharm.D.
Acting Director
Office of Bioequivalence
Office of Generic Drugs

SUBJECT: Decision to waive the requirement for a single, shared system REMS program for alosetron hydrochloride products

This memorandum addresses the merits of a request by Roxane Laboratories, Inc. (Roxane) that FDA waive the requirement for a single, shared system risk evaluation and mitigation strategy (REMS) for alosetron hydrochloride (alosetron) products. Roxane has filed an abbreviated new drug application (ANDA) to market a generic version of Lotronex (alosetron hydrochloride) tablets – a product that was first marketed under a new drug application (NDA) currently held by Prometheus Laboratories, Inc. (Prometheus). The Agency has previously determined that Lotronex tablets require a REMS with elements to assure safe use.[1]

The disposition of Roxane's request is governed by Section 505-1(i)(1)(B) of the Federal Food, Drug & Cosmetic Act (FD&C Act), 21 U.S.C. § 355-1(i)(1)(B), which requires that a generic drug and its listed drug counterpart use a single, shared system (SSS) REMS if a REMS with elements to assure safe use (ETASU) has been required for the listed drug. It also gives FDA the authority to waive this requirement if the Agency determines that the burden of creating a SSS REMS outweighs its benefit.[2] As explained in more detail below, FDA finds that the standard for granting a waiver of the SSS REMS requirement has been met with respect to Roxane's abbreviated new drug application (ANDA) for alosetron because the burden of creating a SSS

[1] See section 505-1 of the Federal Food, Drug, and Cosmetic Act. The currently approved Lotronex REMS can be found on the FDA's Approved REMS website:
http://www fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm

[2] FD&C Act, section 505-1(i)(1)(B)(i).

REMS in these circumstances outweighs the benefits of the SSS REMS. Accordingly, the Agency plans to grant Roxane's waiver request.

To help ensure that this decision does not unduly burden health care providers, patients, or the U.S. healthcare system in general, FDA is attaching two conditions to the grant of the waiver. First, the Agency is requiring that Roxane's waiver-granted REMS system be open to all current and future sponsors of ANDAs or NDAs for alosetron products. Second, FDA is limiting the grant of the waiver to a term of three years. If, at the end of the three year period, Roxane seeks to continue marketing pursuant to the waiver, the Agency will evaluate whether an extension of the waiver is appropriate at that time

I. BACKGROUND

Lotronex (alosetron hydrochloride) (NDA 21-107) was initially approved in February of 2000 for the treatment of irritable bowel syndrome (IBS) in women whose predominant bowel symptom was diarrhea. There are currently no approved generic versions of Lotronex, although FDA has received three ANDAs for alosetron: Roxane Laboratories' ANDA 200652 (received October 16, 2009), Amneal Pharmaceuticals' ANDA 206647 (received (b) (4)), and Par Pharmaceuticals' ANDA 206113 (received (b) (4)). Prometheus listed two patents for Lotronex: U.S. Patent No. 5,360,800 expired on January 13, 2013, and U.S. Patent No. 6,284,770 was held invalid by the United States District Court for the District of New Jersey on May 21, 2014.[3] Lotronex is no longer subject to any form of exclusivity.

a. Statutory Standard

The Agency's authority to waive the requirement for a 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

[3] *Prometheus Labs, Inc. v. Roxane Labs, Inc.*, Case Nos. 11-230 (FSH), 11-1241 (FSH), Unpublished (D.N.J. May 21, 2014) (Hochberg, J.). This ruling is currently under appeal.

. . . .[4]

Thus, FDA may waive the requirement that the reference listed drug (RLD) and any approved ANDA that references the RLD use a SSS REMS, provided the Agency determines (1) that the generic drug's REMS has ETASU that are "comparable" to those of the RLD's REMS, and (2) that the burden of creating a SSS REMS that includes the RLD outweighs the benefit of such a SSS REMS, taking into account the impact on the statutorily-identified stakeholders.

b. The Lotronex REMS

Postmarketing reports of ischemic colitis and serious complications of constipation led the original NDA holder, GlaxoSmithKline (GSK), to voluntarily withdraw Lotronex from the market in November of 2000, after discussions with FDA. In June 2002, FDA subsequently approved a supplemental application for Lotronex under 21 CFR 314, subpart H with a Risk Minimization Action Plan to address the risks of ischemic colitis and serious complications of constipation associated with Lotronex use. Following the passage of the Food and Drug Administration Amendments Act of 2007 (FDAAA), Lotronex was deemed to have in effect an approved REMS, and Prometheus, which had since acquired the NDA for Lotronex from GSK, submitted a proposed REMS for Lotronex in September of 2008. The Lotronex REMS was approved in September of 2010.

The goals of the Lotronex REMS (also known as the "Prescribing Program for Lotronex" or PPL) are (1) to mitigate the risk of ischemic colitis and serious complications of constipation associated with Lotronex use by ensuring that Lotronex is used in only severely affected patients for whom the benefits exceed the risks, and (2) to ensure that the risks of ischemic colitis and serious complications of constipation associated with Lotronex use are communicated to patients, pharmacists, and prescribers. The Lotronex REMS consists of a Medication Guide and several ETASU, which require:

(1) **that healthcare providers who prescribe Lotronex are specially certified in the PPL.**

a. To obtain certification, healthcare providers must attest that they have read the prescribing information for Lotronex and other enrollment materials for the Lotronex REMS, and that they understand (1) the limited population for which Lotronex is approved, (2) the risks associated with Lotronex use, and (3) the specific steps required of them under the REMS to address these risks.

[4] The statute also permits FDA to grant a waiver in situations where the ANDA sponsor has been unable to obtain a license to a protected aspect of the listed drug's REMS. *Id.* § 355-1(i)(1)(B)(ii). That provision does not apply here, as the inability to obtain a license to an aspect of Prometheus' REMS is not at issue.

b. Healthcare providers must also attest that they agree to *take* these steps, which include (among other things) being able to ensure that patients are educated about the benefits and risks of Lotronex, reviewing the contents of the Medication Guide with patients, having patients sign a Patient Acknowledgment Form (PAF), and affixing PPL stickers (showing that the prescriber is certified) to written prescriptions for Lotronex. (The Lotronex REMS requires that *all* Lotronex prescriptions be written: the transmission of Lotronex prescriptions by phone, fax, or computer is not permitted under this REMS program).

(2) that each patient for whom Lotronex is prescribed signs a PAF documenting that certain safe use conditions are in place.

a. By signing the PAF, the patient agrees that she understands the limited population for which Lotronex is approved and the risks associated with Lotronex use, has had her questions about Lotronex treatment answered by her healthcare provider, and will follow the specific instructions in the Medication Guide relating to Lotronex use.

(3) **that pharmacists dispense Lotronex only with documentation of certain safe use conditions**

a. The safe use conditions include (among other things) that pharmacists may only dispense Lotronex in the presence of a written prescription with a PPL sticker and that they will only dispense a 30 day supply with each prescription. Prometheus must perform periodic educational mailings to pharmacists reminding them about their role within the Lotronex REMS and direct pharmacists to educational materials on this topic on the Lotronex PPL website.

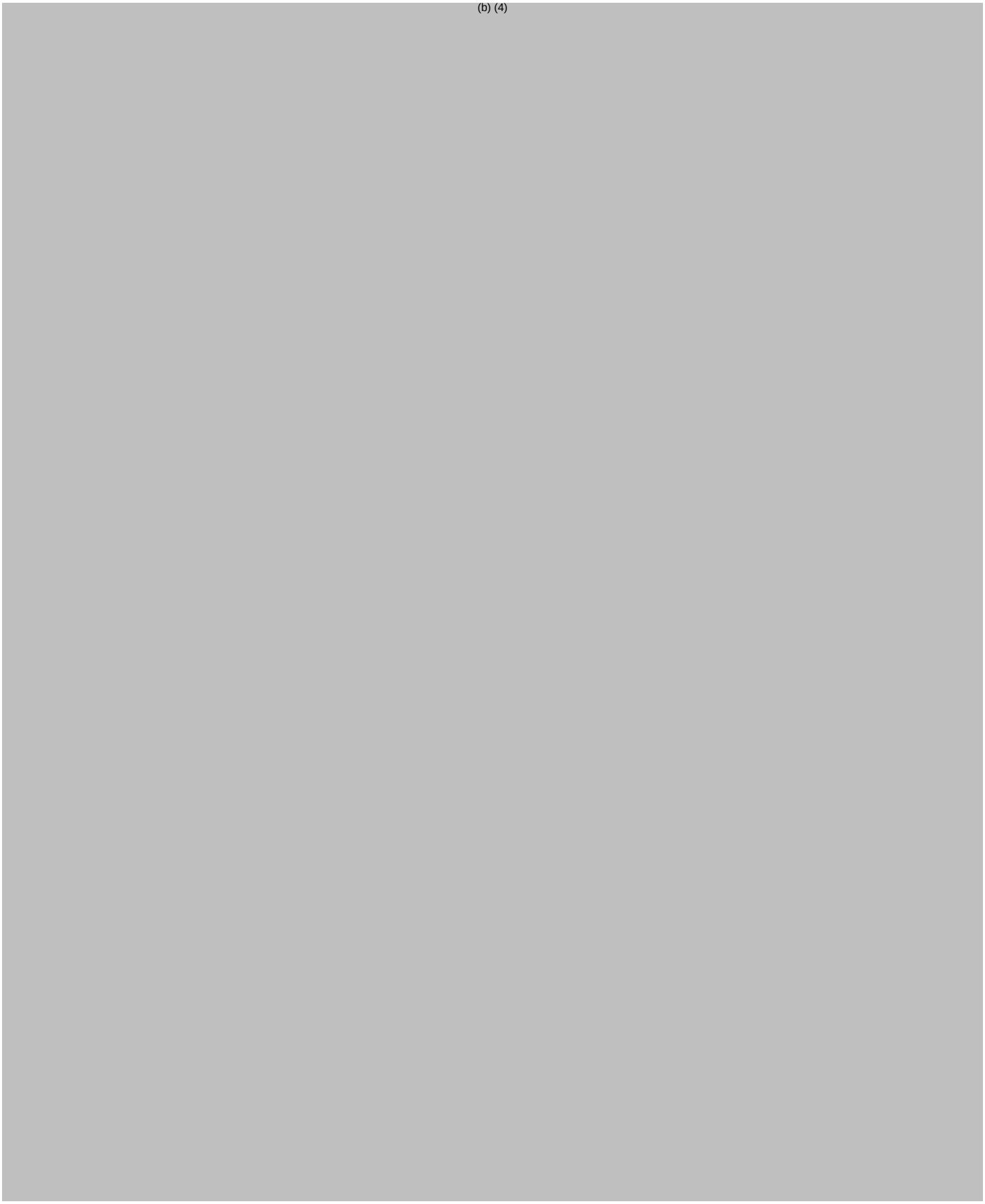
Finally, the REMS also includes an implementation system through which the sponsor evaluates and monitors compliance with the REMS requirements, as well as a timetable for the submission of REMS assessments.

c. Efforts Between Roxane and Prometheus to Establish a SSS REMS for Alosetron Are Unsuccessful

i. Initial Efforts Fail to Result in Meaningful Discussions

(b) (4)

(b) (4)



(b) (4)

Roxane submitted a request for a waiver of the SSS REMS requirement dated March 15, 2013.

(b) (4)

A few months later, in May 2013, Prometheus submitted a citizen petition to FDA arguing (among other things) that it would face increased antitrust scrutiny and product liability uncertainty if it had to negotiate a SSS with its primary competitor (with whom it was engaged in patent litigation) in the absence of a final rule from FDA on SSS standards and processes.[18] FDA's response to Prometheus' petition, issued in October 2013, noted that the Agency continues to consider whether rulemaking would be appropriate in this area, and described the processes that had been used by shared system REMS participants in the past to successfully negotiate and develop these joint systems.[19] The Agency also emphasized that to FDA's knowledge, the Federal Trade Commission (FTC) had not brought a complaint against any of these companies for their negotiation and implementation of shared REMS programs

(b) (4)

[18] The petition also requested that FDA not grant a waiver of the SSS REMS requirement for Lotronex without providing Prometheus adequate notice that a waiver request had been submitted and an opportunity to participate in the process of determining whether to grant the waiver.

[19] Letter Response to Citizen Petition submitted by Prometheus Laboratories, FDA-2013-P-0572 at 5-7 (October 7, 2013) (Prometheus Petition Response).

notwithstanding that they were competitors, and noted that if Prometheus continued to believe it may face antitrust scrutiny for establishing a SSS REMS, it should consult with the FTC.[20]

i. Second Round of Discussions Fails to Result in Negotiated Solution

(b) (4)

[redacted]

[20] Prometheus Petition Response at 6. In addition, the petition response denied Prometheus' request for notice of any SSS waiver requests submitted for Lotronex. The response noted that FDA welcomed input from brand companies at any point on whether the burdens of creating a SSS outweigh the benefits for their drug product, and stated that if Prometheus believed it had information that the Agency should consider on this topic, it should submit such information to its application. As discussed below, Prometheus subsequently submitted a lengthy letter detailing its objections to the granting of a SSS REMS waiver for Lotronex.

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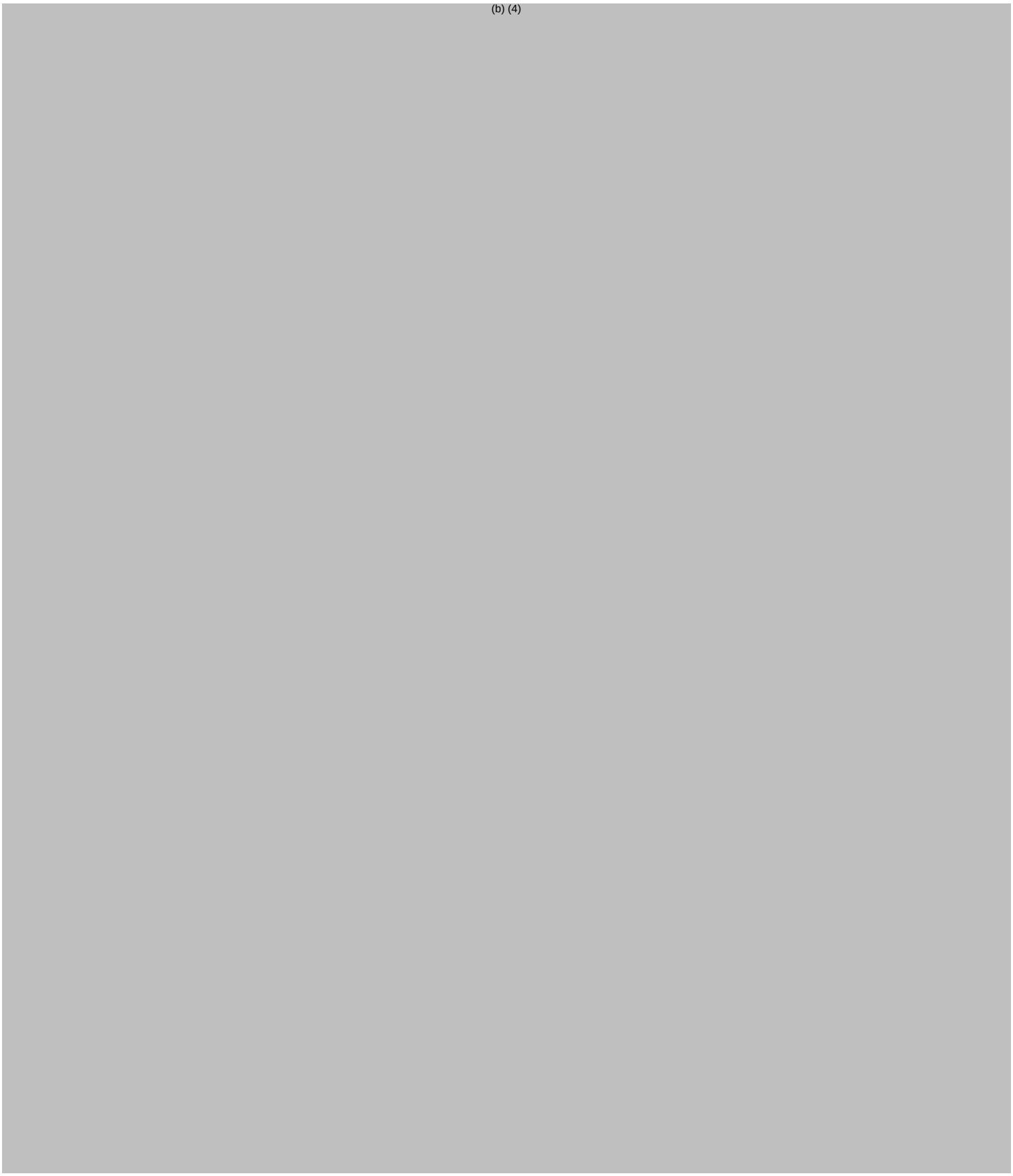

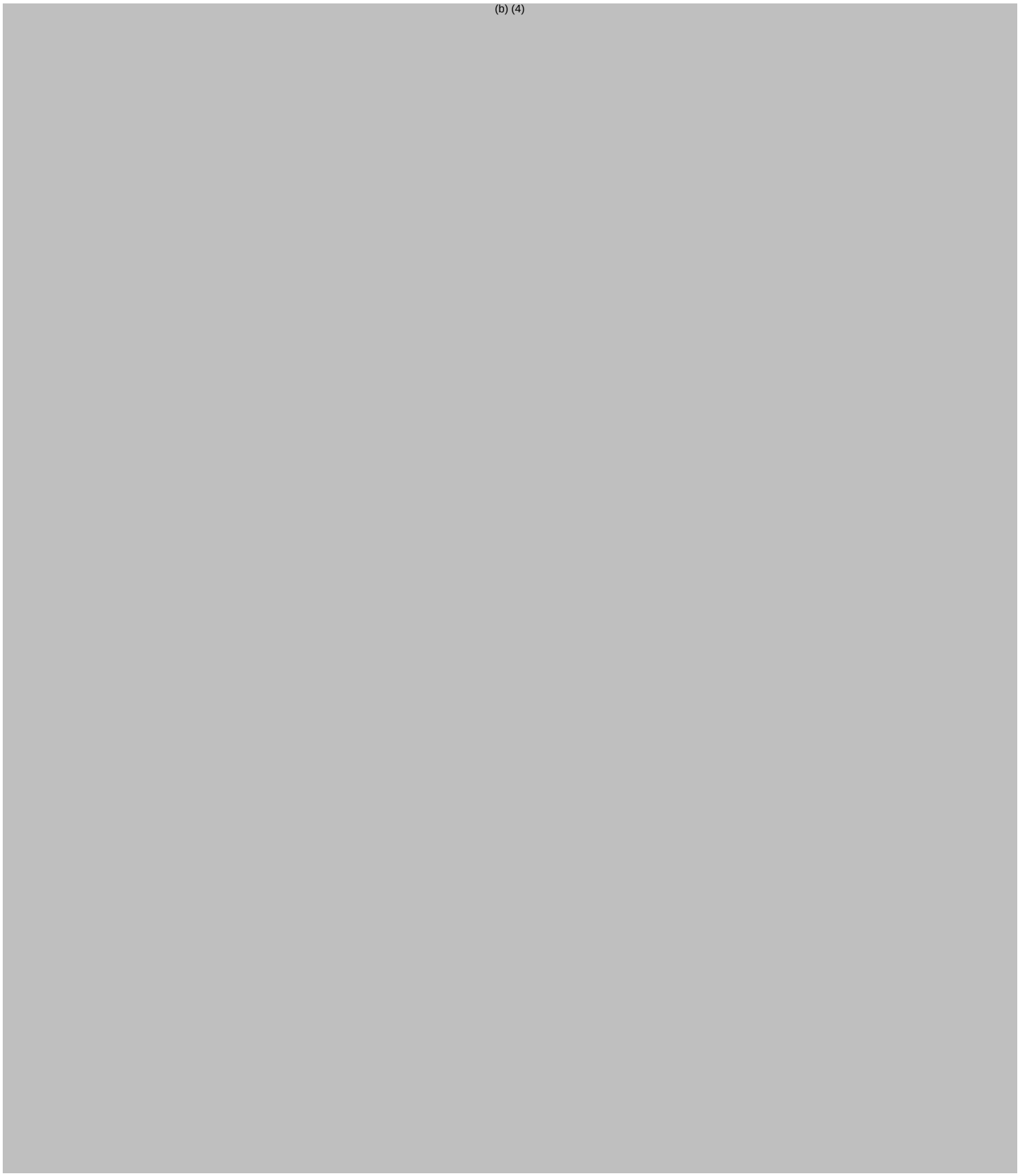
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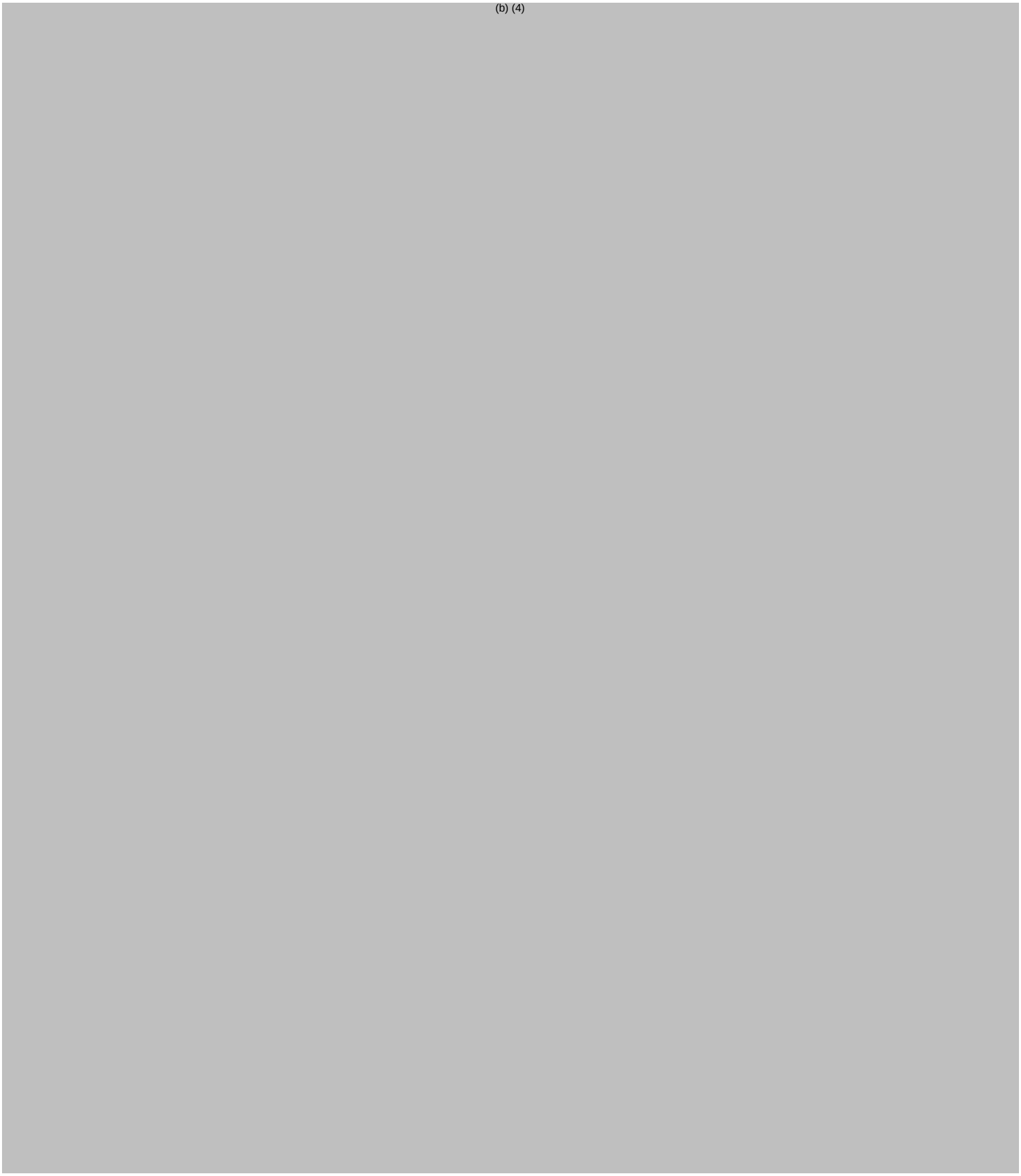

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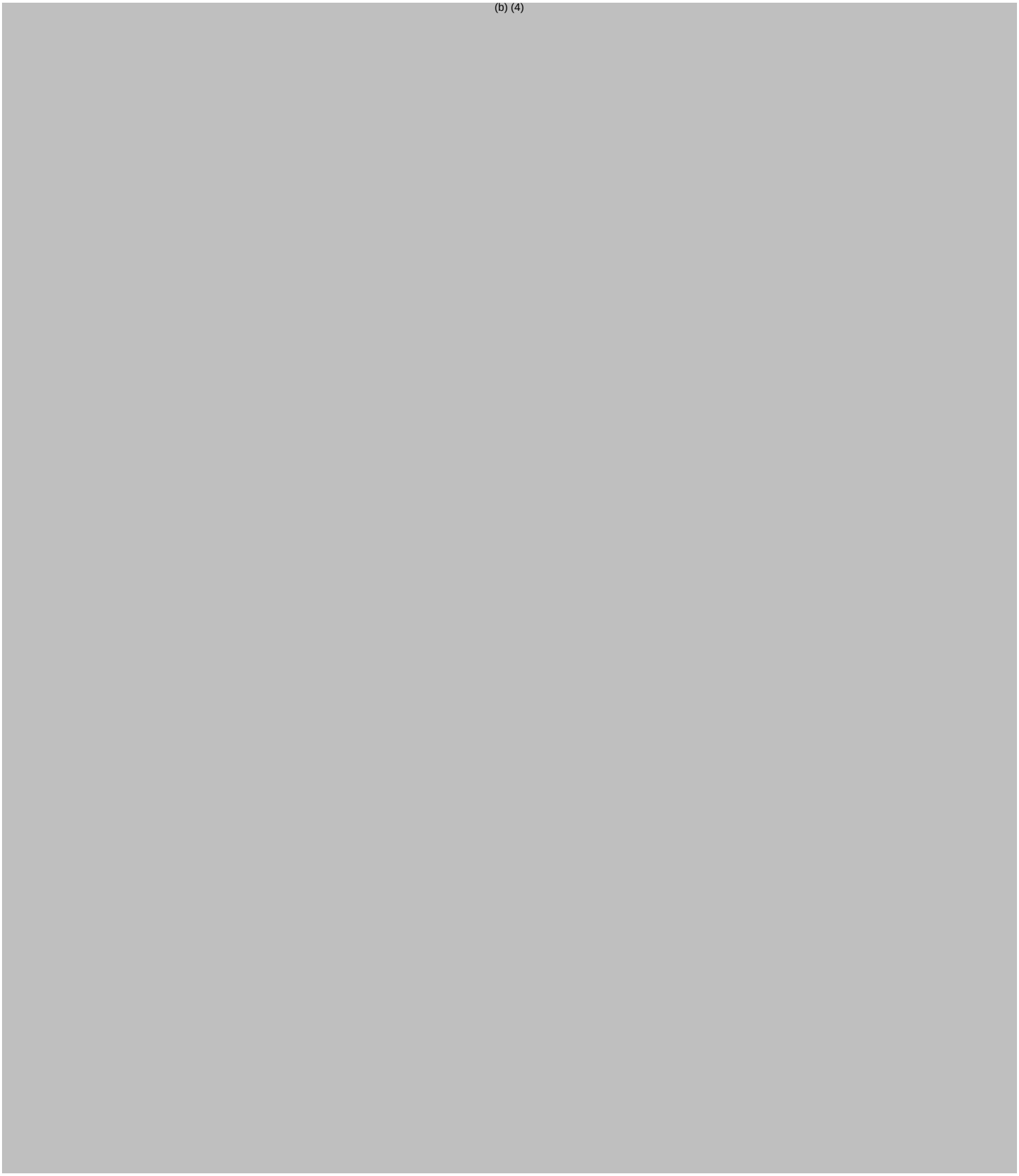
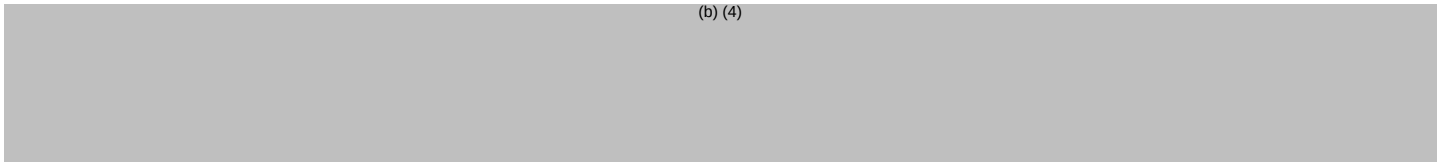


(b) (4)

On September 22, 2014, CDER's REMS Oversight Committee convened to discuss the ongoing Prometheus-Roxane negotiations and Roxane's waiver request, which had been pending since March of 2013. At that meeting, the Committee expressed concern that -- given the length of time that the parties had been negotiating and the pattern of negotiation between them, as well as Prometheus' strong incentive to delay development of a shared REMS for alosetron -- an additional round of FDA-facilitated negotiations would be unlikely to result in the ultimate submission of a SSS REMS for alosetron, and that further efforts to require the parties to negotiate could cause unnecessary delays in the approval of Roxane's ANDA.

(b) (4)



d. Positions of Prometheus and Roxane as to Appropriateness of SSS Waiver

i. Prometheus

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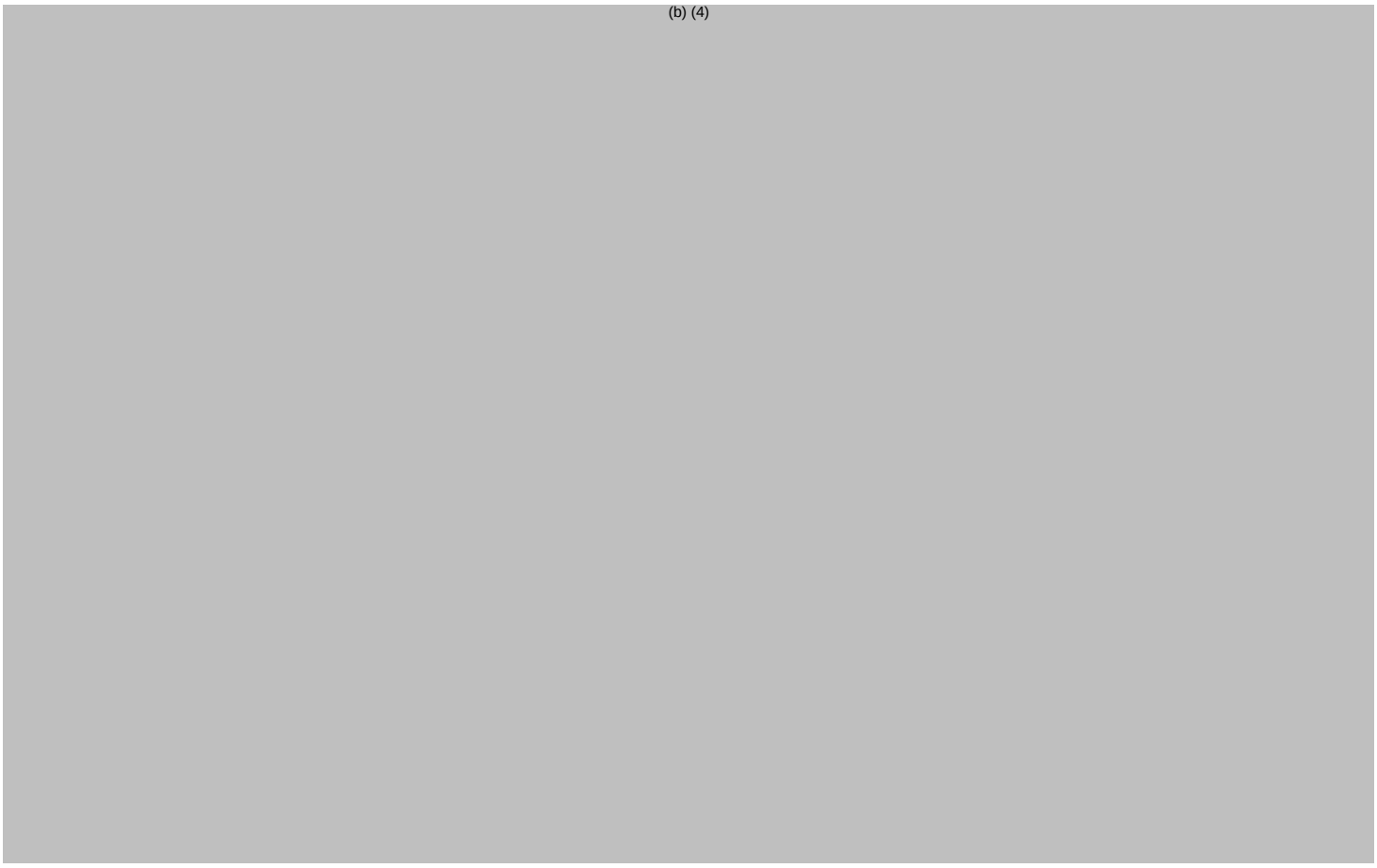

ii. Roxane

(b) (4)

(b) (4)

II. ANALYSIS

Although a SSS REMS for all alosetron products would be ideal, in the more than three years since Roxane and Prometheus first began trying to develop a single, shared system REMS – and despite a substantial investment of time and energy – they have been unable to develop one. And while Prometheus appears to disagree that the parties have reached an impasse in their discussions, SSS negotiations were actively underway for approximately eight months before Roxane concluded that further negotiations were fruitless. The total period of time in which the parties have been attempting to negotiate a SSS REMS for alosetron is substantially longer than the period of time in which the ANDA applicants for Suboxone (buprenorphine-naloxone tablets) attempted to negotiate a SSS REMS with Reckitt Benckiser, the RLD holder for that product, before a SSS waiver was granted.[38] The parties' inability to reach agreement on a SSS REMS threatens to delay the approval of Roxane's pending ANDA, and could delay the approval of other pending ANDAs if it is not resolved soon.

(b) (4)

[38] The waiver of the SSS REMS requirement for the buprenorphine ANDAs is the only previous occasion on which the Agency has waived the SSS REMS requirement. In that case, the ANDA products were approved with a SSS REMS waiver approximately a year after SSS REMS 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) at 6-7 .

We recognize that there are financial incentives and considerations that can hinder companies' efforts to establish a SSS REMS. In the absence of a waiver of the SSS REMS requirement, Roxane and Prometheus' inability to agree to SSS terms and submit a joint SSS REMS could indefinitely delay the approval of a generic version of alosetron.

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 develop a SSS REMS, the Agency has no effective enforcement mechanism to compel Prometheus either to participate in a SSS REMS with Roxane, or to do so on specific terms. The enforcement mechanisms under the FD&C Act are designed to further FDA's public health mission,[39] not to address anticompetitive behavior.

In view of the foregoing, the Agency has decided to grant Roxane's request and waive the SSS REMS requirement for alosetron. As further explained below, this action is appropriate under the legal standard for granting a waiver. Most importantly, a waiver is necessary under the circumstances to ensure that approval of Roxane's pending alosetron ANDA is not indefinitely delayed – thereby denying patient access to an affordable generic version of alosetron.

a. A Waiver Is Appropriate under the Statutory Standard

Roxane has submitted a proposed REMS for its alosetron ANDA that mirrors the current Lotronex REMS. As required by Section 505-1(i)(1)(B) of the FD&C Act, FDA has determined that Roxane's proposed REMS has elements to assure safe use that are comparable to those in Prometheus' approved REMS for alosetron. Indeed, because Roxane's proposed REMS was modeled after Prometheus' approved REMS, Roxane's proposed REMS has the same elements to assure safe use that are included in Prometheus' approved REMS. Roxane's proposed REMS is substantially similar to Prometheus' REMS in all other respects as well.

The Agency has also concluded that the burden of creating a REMS for alosetron products outweighs the benefit of a SSS REMS under the present factual circumstances. The burden associated with creating a SSS REMS for alosetron products is substantial. As described above, more than three years of negotiations between the parties have failed to produce a SSS REMS, and there is little evidence that further negotiations will do so. Given the extensive negotiations

[39] The enforcement tools available to FDA under the REMS provisions are generally designed to ensure the drug's safety . These 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)). None of these mechanisms seem particularly appropriate to require the innovator to work with a generic company to develop a SSS REMS on particular terms.

that have occurred, the inability of the parties to agree to terms, and the Agency's lack of an effective enforcement mechanism to require them to do so, FDA concludes that the burden of creating a SSS REMS in this instance appears to be insurmountably large.

Additionally, the requirement to create a SSS REMS has an indirect burden on patient access to affordable generic alosetron. FDA has been waiting to approve Roxane's pending alosetron ANDA until – and unless – Prometheus and Roxane reach agreement on a SSS REMS. Thus, absent a waiver, patients will be deprived of access to a more affordable generic alosetron product for a potentially infinite time period at a substantial cost to the U.S. healthcare system.

Finally, while there are some benefits to be gained from a SSS REMS, particularly in the form of increased efficiencies for healthcare providers and the Agency, it seems unlikely that these benefits will ever materialize given the inability of the parties to agree to SSS REMS terms. In any event, the Agency finds that these benefits – even if they were to materialize – do not outweigh the significant burdens associated with creating a SSS REMS in these circumstances.

In accordance with Section 505-1(i)(1)(B), the Agency has also considered the impacts that granting a waiver and permitting a second REMS for alosetron will have on health care providers, patients, the ANDA sponsor (Roxane), and the reference drug product holder (Prometheus). The Agency agrees with Roxane that the impacts on these stakeholders favor granting a waiver. While a single shared system would provide benefits to stakeholders by avoiding the potential confusion and inefficiency associated with the co-existence of two REMS for alosetron, these benefits do not outweigh the burden of preventing more affordable generic alosetron from reaching patients. The Agency's findings with respect to the impacts on each stakeholder group are summarized below.

1. Health Care Providers

The existence of two REMS programs may, as Prometheus points out, create some confusion among healthcare providers – for example, as to which version of alosetron can be dispensed with which sticker. To minimize such confusion, however, the Agency intends to require that the ANDA REMS specify that the ANDA product may be dispensed upon the presentation of either sticker.[40] While the agency does not favor the existence of two REMS for alosetron, given that these REMS programs are nearly identical, the Agency does not share Prometheus' level of concern about pharmacist and prescriber ability to implement the two sets of requirements simultaneously. FDA agrees that the existence of two REMS will create some inefficiencies for stakeholders, including the Agency, as a result of the ongoing need for two sets of REMS materials, assessments and modifications. While the imposition of these inefficiencies on the

[40] The ANDA REMS will be approved with this specification; Prometheus may request a corresponding modification of the RLD REMS.

healthcare system is unfortunate, FDA does not believe that the benefit of avoiding these inefficiencies through a SSS REMS outweighs the burden associated with the unavailability of a generic alosetron product.

2. Patients

The Agency finds that a waiver will benefit patients. Mainly, the waiver will permit patient access to a more affordable generic alosetron product. In addition, as required by Section 505-1(i)(1)(B), Roxane's REMS program will have elements to assure safe use that are comparable to those in Prometheus' approved REMS. Thus, Roxane's REMS program should be comparable to Prometheus' REMS in terms of protecting patient safety. While FDA agrees (as noted above) that two REMS will require duplicative sets of materials and may create inefficiencies, the REMS materials under the two programs will contain the same safety messages about alosetron. As a result, FDA does not share Prometheus' view that the co-existence of the two REMS will meaningfully compromise the clarity of the safety messages communicated through the alosetron REMS. In addition, given that the two alosetron REMS programs have comparable requirements, the Agency does not share Prometheus' concern about the potential for a meaningful increase in medical errors under the two REMS.

3. *Roxane*

Absent a waiver, approval of Roxane's pending ANDA will be delayed until Roxane reaches an agreement with Prometheus on a SSS REMS. Prometheus thus has an incentive to delay generic competition by refusing to agree to SSS REMS terms. Prometheus can continue to effectively deny approval of the pending ANDA simply by prolonging the negotiations over a SSS REMS. By granting a waiver, the Agency provides an avenue for Roxane's ANDA to come to market. A waiver will also save Roxane money and man-hours that it may otherwise spend on negotiations with Prometheus. In short, Roxane will benefit significantly from the Agency's decision to grant a waiver.

4. *Prometheus*

From a regulatory perspective, a waiver has virtually no impact on Prometheus. A waiver does not affect Prometheus' ability to continue using its approved REMS, nor does it affect the cost of that REMS. The Agency agrees with Roxane that any competitive harm Prometheus would experience as a result of the market entry of generic alosetron is the result intended under the Hatch Waxman amendments.

b. A Conditional Waiver is Appropriate

FDA is attaching the following conditions to the waiver: (1) the waiver-granted REMS shall be open to all current and future sponsors of ANDAs or NDAs for alosetron,products and (2) the waiver shall be for a three year term that will expire without further action.

The primary purpose of the first condition is to facilitate the Agency's ability to cap the number of REMS for alosetron products at two. FDA will closely monitor compliance with this condition and take appropriate action if there is credible evidence that any future ANDA sponsor is being refused entry into Roxane's waiver-granted REMS program.

The second waiver condition serves two purposes. First, it removes Prometheus' economic incentive not to agree to SSS terms to delay or block generic competition. Second, it creates a limited period of time during which the Agency can monitor the impact on stakeholders of having multiple alosetron REMS. At the end of the three year period, FDA will evaluate the waiver's practical effects and determine whether to extend the waiver or let it expire.

V. Conclusion

For the foregoing reasons, FDA has decided to grant Roxane's request and waive the requirement that alosetron products use a SSS REMS. The waiver shall be conditioned on a requirement that Roxane make its REMS open to all current and future sponsors of ANDAs or NDAs for alosetron products. The waiver shall also be limited to a term of three years.

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/s/

CHANTAL N PHILLIPS
04/29/2015

DALE P CONNER
04/30/2015

MEMORANDUM

DATE: February 19, 2015

TO: The Abbreviated New Drug Applications (ANDAs) for Buprenorphine-Containing Transmucosal Products:

ANDA 090819 – Actavis Elizabeth LLC
ANDA 091422 – Actavis Elizabeth LLC
ANDA 203136 – Amneal Pharmaceuticals
ANDA 090360 – Barr Laboratories, Inc.
ANDA 090622 – Ethylpharm USA Corp.
(b) (4)
ANDA 201066 – Mylan Pharmaceuticals, Inc.
ANDA 078633 – Roxane Laboratories, Inc.
ANDA 203326 – Roxane Laboratories, Inc.
(b) (4)
ANDA 091149 – Teva Pharmaceuticals USA
(b) (4)

FROM: John R. Peters, Acting Director, Office of Bioequivalence, Office of Generic Drugs

SUBJECT: Extension of single shared system REMS waiver for buprenorphine-containing transmucosal products for opioid dependence

The above-listed abbreviated new drug applications (ANDAs) reference listed drugs (Reckitt Benckiser's Suboxone sublingual tablet product (NDA 20-733), (b) (4) , and Subutex sublingual tablet product (NDA 20-732)) that are subject to risk evaluation and mitigation strategies (REMS). The REMS for Suboxone and Subutex are designed to mitigate the risks of accidental overdose, misuse, and abuse of these products and to inform prescribers, pharmacists, and patients of the serious risks associated with these products.

In addition to a Medication Guide, the REMS include two elements to assure safe use (ETASU): (1) a requirement that the drugs be dispensed to patients with evidence or other documentation of safe use conditions, and (2) a requirement that patients using the drugs be subject to certain monitoring.[1]

The Federal Food, Drug & Cosmetic Act (FD&C Act) requires that if the reference listed drug (RLD) has a REMS with ETASU, then any ANDAs must use a single, shared system (SSS) with the listed drug for these ETASU unless FDA waives this requirement.[2] FDA may waive the SSS REMS requirement and permit the ANDA holder to use a different, comparable aspect of the ETASU if the Agency determines that the burden of creating a SSS outweighs the benefits of a SSS, taking into consideration the impact on health care providers, patients, the ANDA applicant, and the RLD holder.[3] As explained in more detail below, FDA finds that the standard for granting a waiver of the requirement for a SSS REMS program continues to be met for buprenorphine-containing transmucosal products for opioid dependence and so the waiver, first granted in February 2013, is extended indefinitely. Specifically, the Agency has determined that the burden of creating a SSS REMS program for these products outweighs the benefit of such a program.

Background

As the attached memo[4] shows, on February 22, 2013, FDA granted a waiver of the requirement for a SSS REMS for buprenorphine-containing transmucosal products for opioid dependence. In a memo regarding that waiver, FDA explained:

> Although an SSSR [SSS REMS] for all buprenorphine-containing transmucosal products is ideal, it is clear that the discussions between Reckitt and the Buprenorphine ANDA Application Holders regarding an SSSR are at an irresolvable impasse….There appears to be little FDA can do to end the standoff between the two sides, however, because

[1] The REMS also include requirements for an implementation system and a timetable for the submission of REMS assessments.

[2] Section 505-1(i)(1)(B) of the FD&C Act (21 USC § 355-1(i)(1)(B)).

[3] Section 505-1(i)(1)(B)(i) of the FD&C Act. FDA may also waive the SSS requirement in other circumstances not applicable here.

[4] See Appendix, Memorandum re: Decision to waive the requirement for a single, shared system REMS for buprenorphine-containing transmucosal products (submitted to ANDA 090819, et al. – the Buprenorphine ANDA application holders at the time the waiver was granted -- February 22, 2013) (Buprenorphine Waiver Memo); see also waiver approval letter from Gregory P. Geba, Director, Office of Generic Drugs (issued to ANDA 090819, et al.)(February 22, 2013).

> although the Act mandates that the innovator and the generic companies develop an SSSR, the Agency has no effective enforcement mechanism to compel Reckitt to participate in an SSSR with the Buprenorphine ANDA Application Holders. The enforcement mechanisms under the FD&C Act are designed to further FDA's public health mission, not to address anticompetitive behavior.
>
> In view of the foregoing, the Agency has decided to grant the Buprenorphine ANDA Application Holders' requests and waive the SSSR requirement for buprenorphine-containing transmucosal products. As further explained below, FDA believes this action is appropriate under the legal standard for granting a waiver. More importantly, the Agency believes a waiver is necessary under the circumstances to ensure that Reckitt does not indefinitely delay approval of the pending buprenorphine ANDAs – and deny patient access to affordable generic drug products in the process – by refusing to cooperate with the Buprenorphine ANDA Application Holders on the development of an SSSR.[5]

Consistent with the standard for granting a waiver set forth in section 505-1(i)(1)(B) of the FD&C Act, FDA determined that the waiver-granted REMS that would be used by the Buprenorphine ANDA Application Holders[6] would be comparable to the one in place for the RLD,[7] and that the burdens of creating a single shared system outweighed the benefits of creating one:

> The burden associated with creating an SSSR for buprenorphine-containing transmucosal products is substantial. Reckitt has insisted on resolving the liability, cost-sharing, and other ancillary "gating issues" before it will even consider joining an SSSR with the Buprenorphine ANDA Application Holders. Although similarly complex issues arose in the other instances where FDA has required an SSSR, the innovators and generic manufacturers in those instances were able to work through the issues and create an SSSR. Here, however, Reckitt and the Buprenorphine ANDA Application Holders are no closer to resolving their differences over the SSSR than they were when they started negotiating in early 2012…Given the extensive negotiations that have occurred, Reckitt's pattern of conduct, and the Agency's lack of an effective enforcement mechanism to require Reckitt and the Buprenorphine ANDA Application Holders to agree to an SSSR,

[5] Buprenorphine Waiver Memo at 10-11 (citations omitted).

[6] This REMS is referred to as the "Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD) REMS."

[7] Buprenorphine Waiver Memo at 11.

> FDA concludes that the burden of creating an SSSR in this instance is insurmountably large.
>
> …
>
> In contrast, there is little benefit to be gained from an SSSR. Although an SSSR might reduce the price of buprenorphine drugs, or at least the cost of administering related healthcare services, it is highly unlikely that either benefit with ever materialize given the standstill in negotiations between Reckitt and the Buprenorphine ANDA Application Holders. Moreover, the value of such a benefit would be minimal. In large part, this is because both the proposed and existing buprenorphine REMS (i.e., the ANDA sponsors' proposed REMS program and Reckitt's approved REMS for Subutex and Suboxone sublingual tablets) lack restrictive elements, such as enrollment or certification requirements, or controls on distribution, prescribing, and dispensing. Consequently, prescribers and pharmacists can participate in all the REMS without developing and implementing duplicative and costly administrative systems for each REMS. The creation of an SSSR for all buprenorphine-containing transmucosal products thus would not result in substantial cost savings and other administrative efficiencies for these stakeholders.[8]

FDA imposed a time limitation on the waiver, however, stating in the memo that "the waiver shall be for a two-year term that will expire without further action."[9] The two year term of the original waiver expires on February 22, 2015. The time limitation was to serve two purposes:

> First, it removes Reckitt's economic incentive to use lack of cooperation with the SSSR to delay or block generic competition. Second, it creates a limited period of time during which the Agency can monitor the impacts on stakeholders of multiple buprenorphine REMS. At the end of the two-year period, the Agency will evaluate the waiver's practical effects and determine whether to extend the waiver or let it expire. FDA is hopeful that Reckitt and the Buprenorphine ANDA Application Holders will agree on an SSSR before the end of the period, particularly since Reckitt will no longer have an incentive to use the SSSR requirement as a tool to exclude competition once the waiver is issued and generic competition is established.[10]

[8] Id. at 11-12.

[9] Id. at 14.

[10] Id.

FDA's Determination Regarding Waiver Extension

In August of 2014, the members of the Buprenorphine Products Manufacturers Group (BPMG)[11] sent an email to FDA requesting that the Agency indefinitely extend their waiver. The Agency responded by asking about the status of discussions with Reckitt Benckiser (Reckitt) regarding the development of a SSS REMS. The BPMG members indicated that there had been no further communications with Reckitt regarding SSS REMS development, and requested that FDA facilitate any further discussions on this topic. FDA subsequently held a teleconference with representatives from the BPMG and Reckitt on December 4, 2014, in an effort to assist in resolving the impasse regarding the development of a SSS REMS. At the start of that call, Reckitt informed FDA and the members of the BPMG that it was being investigated by the FTC in connection with its conduct during buprenorphine SSS negotiations, and that Reckitt had therefore been advised by its counsel not to participate in additional buprenorphine SSS REMS discussions.

Because of Reckitt's refusal to participate in further SSS REMS discussions, the parties remain unable to resolve their impasse regarding SSS terms. The burden associated with creating a SSS therefore continues to be – as it was at the time of the grant of the original waiver – substantial, and perhaps insurmountable.[12] The benefits of a SSS REMS, on the other hand, remain minimal, as the REMS programs do not contain restrictive elements (such as enrollment or certification requirements, or controls on distribution, prescribing, and dispensing). As a result, prescribers and pharmacists continue to be able to participate in both REMS without developing and implementing duplicative administrative systems for each REMS.

Finally, none of the information obtained through FDA's review of buprenorphine utilization data, REMS assessments of the BTOD, Suboxone and Subutex REMS, FDA Adverse Event Reporting System (FAERS) data, FDA's inquiries to members of the Drug Safety Board, or other sources has suggested that the operation of two parallel REMS programs for buprenorphine-containing transmucosal products for opioid dependence imposes burdens on the healthcare system significant enough to outweigh the burdens associated with the elimination of the waiver for the BTOD products. Rather, utilization statistics for these products suggest that

[11] The BPMG includes the ANDA application holders of buprenorphine-containing transmucosal products for opioid dependence in the waiver-granted BTOD REMS, as well as two NDA holders of buprenorphine-containing transmucosal products for opioid dependence (NDA 204242 and 205637) that are also part of the BTOD REMS).

[12] Buprenorphine Waiver Memo at 12.

the waiver of the SSS REMS requirement has allowed patients to make increasing use of lower cost generic buprenorphine products.[13]

Accordingly, for the reasons stated herein (and in the original Buprenorphine Waiver Memo, appended), FDA has determined that the statutory standard for granting a waiver of the SSS REMS requirement continues to be met in the case of buprenorphine-containing transmucosal products for opioid dependence. The Agency is therefore extending, indefinitely, the SSS waiver for buprenorphine-containing transmucosal products for opioid dependence. The requirement that the BTOD REMS remain open to all current and future sponsors of buprenorphine-containing transmucosal products for opioid dependence will continue to be a condition of this waiver.

[13] See Nationally estimated number of buprenorphine and buprenorphine/naloxone tablets/film prescriptions dispensed through U.S. outpatient retail pharmacies 1/2011 – 7/2014, monthly. Source: IMS Health, National Sales Perspective (NSP). Jan 2011 – July 2014. Extracted August 2014.

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/s/

CHANTAL N PHILLIPS
02/19/2015

JOHN R PETERS
02/19/2015