DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

OCT 7 2013

William Franzblau
Vice President, Legal Affairs
Prometheus Laboratories, Inc.
9410 Carroll Park Drive
San Diego, CA 92121

Re: Docket No. FDA-2013-P-0572

Dear Mr. Franzblau:

This letter responds to Prometheus Laboratories, Inc.'s (Prometheus) citizen petition received on May 10, 2013 (Petition). In the Petition, Prometheus requests that the Food and Drug Administration (FDA or Agency) (1) complete notice and comment rulemaking to establish standards and processes for single, shared risk evaluation and mitigation strategy (REMS) systems, and (2) refrain from granting a waiver of the single, shared system requirement for Lotronex without providing Prometheus with adequate notice that a waiver request was submitted and an opportunity to participate in the process of determining whether the waiver should be granted (Petition at 1-2).

FDA has carefully considered the information submitted in the Petition and other relevant information available to the Agency. Based on our review of these materials and for the reasons described below, the Petition is granted in part and denied in part.

I. BACKGROUND

A. Lotronex

Prometheus is the new drug application (NDA) holder for Lotronex[1] (alosetron hydrochloride), which was approved by FDA in February 2000. Lotronex is indicated for women with severe, diarrhea-predominant irritable bowel syndrome (IBS) who have chronic IBS symptoms, have not responded adequately to conventional therapy, and have had anatomic or biochemical abnormalities of the gastrointestinal tract ruled out. Due to risks of infrequent (but serious) gastrointestinal adverse reactions (including ischemic colitis (IC) and serious complications of constipation (CoC)) associated with Lotronex use, Lotronex is subject to a REMS designed to help ensure that it is used only in severely affected patients for whom the benefits exceed the risks, and that the risk of IC and serious CoC are communicated to patients, pharmacists, and prescribers.

[1] NDA 21-107.

The REMS for Lotronex consists of a Medication Guide and several elements to assure safe use (ETASU), which require (1) that healthcare providers who prescribe Lotronex are specially certified, (2) that each patient prescribed Lotronex signs a Patient Acknowledgement Form documenting that certain safe use conditions are in place, and (3) that pharmacists dispense Lotronex only with documentation of certain safe use conditions. 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.

Prometheus acquired the NDA for Lotronex from GlaxoSmithKline in January 2008. There are currently no approved generic versions of Lotronex. Roxane Laboratories, Inc. (Roxane) has submitted an abbreviated new drug application (ANDA)[2] for this product, and has been in discussions with Prometheus over the establishment of a single, shared system REMS for the generic and brand versions.[3]

B. Legal and Regulatory Framework

1. Abbreviated New Drug Applications

The ANDA approval process established by the Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments) is set forth in section 505(j) of the Federal Food, Drug & Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)). To obtain approval, an ANDA applicant is not required to submit evidence establishing the clinical safety and effectiveness of the drug product; instead, an ANDA relies on FDA's previous finding that the reference listed drug (RLD)[4] is safe and effective. To rely on a previous finding of safety and effectiveness, an ANDA applicant must demonstrate, among other things, that its drug product is bioequivalent to the RLD (section 505(j)(2)(A)(iv) of the FD&C Act). In addition, an ANDA must contain, with certain exceptions not relevant here, information to show that the proposed drug has the same active ingredient(s), indications for use, route of administration, dosage form, strength, and labeling as the RLD (section 505(j)(2)(A) of the FD&C Act).

2. Approval of Drug Products with REMS

Section 505-1(a) of the FD&C Act (21 U.S.C. 355-1(a)) authorizes FDA to require applicants[5] to submit a proposed REMS when FDA has determined that a REMS is necessary to ensure that the

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[2] ANDA 20-0652.

[3] See Petition at 6; Transcript of the July 10, 2013, Meeting of the Drug Safety and Risk Management Advisory Committee Meeting at 223-226, available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM366931.pdf.

[4] A *listed* drug is a drug that FDA has approved (21 CFR 314.3). A *reference listed drug* is an approved drug that is referenced by an ANDA applicant as a basis for approval of that ANDA (id.).

[5] Section 505-1 of the FD&C Act applies to any application for approval of a prescription drug submitted under section 505(b) or (j) of the FD&C Act (thus including both NDAs (including those submitted under section 505(b)(2)) and ANDAs submitted under 505(j)), as well as applications submitted under section 351 of the Public Health Service Act (section 505-1(b)(2) of the FD&C Act, which references section 505(p)(1)(A)).

benefits of a drug outweigh its risks. A REMS is a required risk minimization strategy that employs tools beyond routine professional labeling (such as Medication Guides, patient package inserts, and/or communication plans) to ensure that the benefits of a drug outweigh its risks (section 505-1(e) of the FD&C Act). FDA may also require certain "elements to assure safe use" (ETASU) when additional elements are necessary to mitigate specific serious risks associated with a drug (section 505-1(f)(3) of the FD&C Act). ETASU may include, for example, requirements that healthcare providers who prescribe the drug have particular training or experience, that patients using the drug be monitored, or that the drug be dispensed to patients with evidence or other documentation of safe use conditions (id.).

If the RLD is subject to a REMS, ANDAs referencing it must have the same Medication Guide[6] if there is one and the same or comparable ETASU (section 505-1(i)(1) of the FD&C Act). Section 505-1(i)(1)(B) of the FD&C Act requires that ANDAs use a "single, shared system" with the RLD for any ETASU unless a waiver of this requirement has been granted. The statute permits waiver of the single, shared system requirement "if the burden of creating a single, shared system outweighs the benefits 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."[7] If a waiver of the single, shared system requirement is granted, the ANDA may use "a different, comparable aspect of the [ETASU]," instead of participating in a single, shared system with the RLD.

Finally, the FD&C Act provides that "no holder of an approved covered application shall use any [ETASU] required by the Secretary under this subsection to block or delay approval of [a 505(b)(2) application or an ANDA] or to prevent application of such element under subsection (i)(l)(B) to a drug that is the subject of an [ANDA]" (Section 505-1(f)(8) of the FD&C Act).

II. DISCUSSION

A. Prometheus Petition

Prometheus' Petition requests that the Agency complete notice and comment rulemaking to establish standards and processes for single, shared system REMS, including the following:

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[6] Medication Guides, which are part of approved labeling (see 21 CFR 208), are subject to the FD&C Act's same labeling requirement (as well as its exceptions). Medication Guides may also be part of a REMS (see section 505-1(e)(2) of the FD&C Act).

[7] The statute also permits waiver of the single, shared system requirement where:

> an aspect of the [ETASU] 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 [ANDA] certifies that it has sought a license for use of an aspect of the [ETASU] for the applicable listed drug and that it was unable to obtain a license.

Section 505-1(i)(1)(B)(ii) of the FD&C Act.

(1) the process that FDA will follow to inform sponsors of the obligation to negotiate a shared REMS, and the other parties that must be included in any shared REMS;
(2) the aspects of a REMS that must be shared for a REMS to be considered a single, shared REMS under the FD&C Act;
(3) the regulatory obligations of the parties to a single, shared REMS, including obligations for performance of the REMS elements, adverse event reporting, and assessment of the REMS;
(4) the approval and modification process for single, shared REMS, including the process for adding additional sponsors to the REMS; and
(5) the process for consideration of a waiver from the requirement for a single, shared REMS and the standard that must be met before FDA will grant a waiver.

(Petition at 1-2). Prometheus argues that the FD&C Act's requirement that ANDAs and RLDs use a single, shared system for any ETASU is "unprecedented among federal laws" to the extent that it requires competitors "to negotiate and reach an agreement with a specific identified competitor and work together as business partners for the foreseeable future" (Petition at 7).

The Petition points out that FDA has not issued regulations or guidance on single, shared systems (Petition at 7-8), argues that there is little shared system precedent to guide sponsors attempting to negotiate a single, shared system, and notes that these negotiations are especially challenging when the brand and generic companies are engaged in patent litigation (Petition at 9-10). In particular, Prometheus believes that FDA guidance is lacking with respect to when single shared system negotiations are expected to take place relative to the ANDA approval and patent litigation process, how costs and other responsibilities are to be shared among single, shared system participants, and what criteria FDA will use to determine that a brand company's failure to agree to single, shared system terms constitutes blocking or delaying of generic competition under the prohibition set forth in the FD&C Act, among other things (Petition at 8). Without a final rule on single, shared systems, Prometheus stresses that brand companies face significant resource commitments and uncertain risks arising from antitrust law and product liability (Petition at 11).

The Petition also requests that FDA refrain from granting a waiver of the single shared REMS requirement for Lotronex unless FDA provides Prometheus with adequate notice that a waiver request has been submitted and an opportunity to participate in the process of determining whether the waiver should be granted (Petition at 2). Prometheus argues that the FD&C Act requires FDA to consider the impact of a single shared system waiver on the sponsor of the reference drug product, and that the sponsor is the only party that can accurately inform FDA about the impact a waiver will have on it (Petition at 16-17). Prometheus contends that FDA must inform it of any waiver request that is submitted so that (1) it can provide FDA with information that may be relevant, and (2) it will be aware of whether the generic company is negotiating the terms of a single, shared system in good faith (Petition at 17).

B. Request for Rulemaking on Single, Shared System Processes and Standards

To the extent that Prometheus' Petition takes issue with the FD&C Act's requirement that brand and generic companies work together to implement single, shared REMS systems, we note that this requirement is statutorily mandated by Congress. The single, shared system provision of the FD&C Act was designed to eliminate duplicative systems to implement ETASU requirements, which can place added burdens on the healthcare system. As FDA gains experience with single, shared system development, the Agency is considering whether regulations or guidance in this area would assist industry with the development and implementation of these systems. We describe below how single, shared systems have been successfully developed in the past, which we hope will provide useful information with respect to some of the issues raised in Prometheus' Petition.

When a generic application for a product subject to a REMS with ETASU has been found to be acceptable for filing, FDA has notified the ANDA applicant of the requirement for a single, shared system through a REMS notification letter, which has directed the ANDA applicant to contact the sponsor of the RLD regarding the development of a single, shared system REMS.[8] FDA has expected that negotiation of the single, shared REMS would begin promptly thereafter, and would proceed concurrently with the review of the ANDA application.

In cases where several companies were impacted by the single, shared REMS requirement, many companies have chosen to form what is commonly referred to as an "industry working group" (IWG) that has worked together to develop a proposal for the single, shared REMS. In the past, FDA has instructed the IWG sponsors to identify a single point of contact to represent the IWG, and emphasized the importance of first working out the applicable cost and governance structures. FDA has typically monitored the IWG's progress on developing a REMS through regular teleconferences and face-to-face meetings on an as-needed basis. In addition to monitoring the IWG's progress on developing a REMS, FDA has acted to help ensure that sponsors were cooperating and that there were no obstacles to developing a single, shared system. When a company indicated to the Agency that another company (brand or generic) was not receptive or responsive to such efforts, the Agency has held teleconferences, individually and jointly, with firms involved, and/or has asked them to come to FDA for face-to-face discussions to help facilitate resolution of any issues that were preventing moving forward on a single, shared system.

Once developed, the single, shared REMS proposal has been submitted by the brand and generic companies to the Agency for review. The proposed single, shared REMS developed by the brand and generic sponsors was then reviewed as part of the overall ANDA review process (and,

[8] When FDA has determined that a REMS with ETASU is necessary for a drug product for which ANDAs are already approved, NDA and ANDA holders have each been notified of the single, shared system requirement. In such cases, the proposed REMS developed by the NDA and ANDA sponsors has been reviewed as a supplement to each affected application.

where appropriate, approved as part of the overall ANDA approval).[9] Agency REMS review teams have been multidisciplinary and have involved staff from a number of offices including the Office of Surveillance and Epidemiology, the Office of New Drugs, the Office of Generic Drugs, the Office of Compliance, the Office of Regulatory Policy, and the Drug Safety Operations staff within Office of Center Director. Others within the Agency have been consulted as needed.

To help reduce the burden on the healthcare system, FDA has previously required that all components of a REMS program be shared by the participating sponsors in a shared system REMS. That is, NDA and ANDA application holders in a single, shared system REMS have been subject to the same ETASU, implementation system, and assessments.[10] In addition, participating sponsors have worked together to establish a common REMS document and REMS materials (for example, common forms, training materials, and a common REMS Web site and database to capture entities enrolled in the REMS, such as hospitals, pharmacies, and healthcare professionals).

Unlike the elements of the REMS, which are reviewed and approved by FDA, cost-sharing, governance, and other business issues relating to the implementation of single, shared REMS are left to the discretion of the sponsors. Competitor brand and generic companies have negotiated shared system REMS or risk management systems for numerous products, including mycophenolate, isotretinoin, rosiglitazone, extended-release and long-acting opioid analgesics, and transmucosal immediate-release fentanyl products. Notwithstanding that they were competitors, resolution of these issues did not prove unattainable for these parties. Further, to FDA's knowledge, the Federal Trade Commission (FTC) has not brought complaints against any of the companies involved in connection with the negotiation and implementation of these REMS. To the extent that Prometheus believes there may be antitrust issues associated with establishing single, shared systems, we suggest it consult with the FTC.[11]

Thus far, once a single shared REMS is approved, FDA has required changes proposed by a sponsor affecting common content be agreed to by the other participating sponsors in the REMS and then submitted to each of the individual applications. Generally, for product-specific changes (such as the addition of a new indication), the change has first been approved under the individual application, after which the other participating sponsors in the REMS have been notified that a change to their REMS was necessary. When a new product has been added to a single, shared system, the participants in the REMS generally each have submitted the

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[9] As noted above, when FDA has determined that a REMS with ETASU was necessary for a product for which ANDAs were already approved, the proposed single shared REMS developed by NDA and ANDA sponsors was reviewed as a supplement to each affected application.

[10] ANDA applicants have agreed to be included in the shared assessment. We note that Medication Guides are product-specific, so even if a REMS includes a Medication Guide, this component of the REMS is not technically "shared" by participating sponsors in the REMS (though, as discussed above, Medication Guides are subject to the FD&C Act's same labeling requirement).

[11] See 16 CFR 1.1 et seq.; see also *Guidance From Staff of the Bureau of Competition's Health Care Division on Requesting and Obtaining an Advisory Opinion* (May 2010), available at http://www.ftc.gov/bc/healthcare/industryguide/adv-opinionguidance.pdf.

modification (adding the new product) to their individual applications once the new product was approved. We note that FDA is in the process of developing guidance on the process for modifying REMS. Finally, FDA has evaluated waivers of the single, shared system requirement on a case-by-case basis to determine whether the burdens of creating a particular single, shared system outweigh its benefits, considering the impact on healthcare providers, patients, the ANDA applicant, and the RLD holder (section 505-1(i)(1)(B)(i) of the FD&C Act).

As indicated above, as FDA gains experience with single, shared system development, it is evaluating whether notice and comment rulemaking or guidance on single, shared systems would be appropriate. To the extent that Prometheus' Petition requests that the Agency engage in rulemaking on this matter at this time, your request is denied.

C. Request for Notice of Single, Shared System Waiver Requests for Lotronex and Opportunity to Participate in Determination as to Whether Waivers Are Granted

We deny Prometheus' request that FDA provide you with notice of any single, shared system waiver requests submitted for Lotronex.

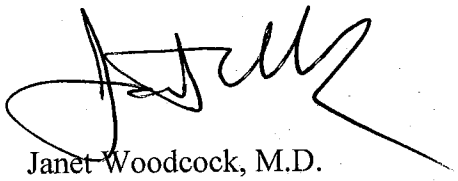
With respect to Prometheus' request for an opportunity to participate in the process of determining whether the single, shared system requirement should be waived for Lotronex, we note that FDA welcomes input from brand companies at any point on whether the burdens of creating a single, shared system outweigh the benefits for their drug product. In the past, through its facilitation of single, shared system negotiations between brand and generic companies, FDA has received general information about brand companies' views on burdens to the companies involved and other single, shared system issues. Brand companies are also free to provide FDA with input about the appropriateness of a single, shared system for their product's REMS outside of the negotiation process, and have done so. In certain circumstances, if FDA believes additional information from the brand company is necessary to complete its evaluation of the burdens and benefits of creating a particular single, shared system, FDA may also solicit input from the brand company on this topic. Moreover, the Agency may determine on its own that waiver of the single, shared system requirement is appropriate for a particular product without having received a waiver request from one of the parties. If Prometheus believes it has information that the Agency should consider on this topic, it should submit such information to its application. Last, we note that FDA has invited Prometheus and Roxane to the Agency to discuss the development of a single, shared system for Lotronex, which will provide both parties an additional opportunity to express their views to the Agency about any single, shared system issues, including the possibility of a waiver.

III. CONCLUSION

For the reasons described above, Prometheus' request that the Agency complete notice and comment rulemaking to establish standards and processes for single, shared systems is denied at this time. The Agency is continuing to evaluate whether rulemaking or guidance relating to single, shared system standards and processes would be useful in the development and

implementation of these systems. Prometheus' request that FDA provide it with notice of any single, shared system waiver requests submitted for Lotronex is also denied. Its request that FDA provide it with an opportunity to participate in the process of determining whether to grant a waiver of the single, shared system requirement for Lotronex is granted to the extent that FDA welcomes Prometheus' input on this topic at any time.

Sincerely,



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