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May 10, 2013

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

CITIZEN PETITION

The undersigned, on behalf of Prometheus Laboratories Inc. (Prometheus), submits this petition under Sections 502, 505, and 527 of the Federal Food, Drug, and Cosmetic Act (FDCA), 21 C.F.R. § 10.30, and other provisions of law. Prometheus respectfully requests that the Commissioner of Food and Drugs (Commissioner) provide meaningful direction to industry engaged in negotiating single shared Risk Evaluation and Mitigation Strategies (REMS) through notice and comment rulemaking establishing the standards and processes for single shared REMS and waivers from the requirement for a single shared REMS. In addition, Prometheus requests that it be given notice and the opportunity to participate in any process used by the Food and Drug Administration (FDA) to determine whether to grant a waiver from the requirement for a single shared REMS for Lotronex.

ACTIONS REQUESTED

The undersigned requests that the Commissioner take the following actions:

- Complete notice and comment rulemaking establishing the standards and processes for single shared REMS including the following:
    - the process that will be followed by the agency to inform sponsors of the obligation to negotiate a shared REMS and the other parties that must be included in any shared REMS;
    - the aspects of a REMS that must be shared for a REMS to be considered a single shared REMS under the FDCA;
    - 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;
    - the approval and modification process for single shared REMS, including the process for adding additional sponsors to the REMS; and

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- 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.

- Do not grant a waiver to any sponsor from the requirement for a single shared REMS for Lotronex without providing Prometheus, the sponsor of Lotronex, adequate notice that a waiver request has been filed and an opportunity to participate in the process of determining whether to grant the waiver and permit a sponsor of an Abbreviated New Drug Application (ANDA) to use a different but comparable aspect of the elements to assure use required for Lotronex.

STATEMENT OF GROUNDS

I. BACKGROUND

A. Irritable Bowel Syndrome

Irritable Bowel Syndrome (IBS) is a chronic gastrointestinal disorder that affects approximately 5-20% of the western population.[1] Between 70-75% of IBS sufferers are female.[2] There are different classifications of IBS, including: (1) diarrhea-predominant (IBS-D); (2) constipation-predominant (IBS-C); and (3) IBS with alternating stool pattern (IBS-A or pain-predominant).[3]

IBS is not life threatening, but can greatly affect the quality of life of sufferers. Pain, fatigue, and other symptoms often prevent IBS sufferers from working, traveling, and socializing. According to a survey conducted by the International Foundation for Functional Gastrointestinal Disorders, 61% of respondents with severe IBS were considered to have clinical anxiety.[4] Moreover, in a longitudinal outcomes study of patients with IBS, patients reported a nearly 35% overall work productivity loss.[5]

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[1] Magnus Halland & Nicholas J. Talley, *New treatments for IBS*, 10 NAT. REV. GASTROENTEROL. HEPATOL., 13 (Jan. 2013), *available at* http://www.nature.com/nrgastro/journal/v10/n1/pdf/nrgastro.2012.207.pdf (attached as Exhibit 1).

[2] K.D. Bardhan et al., *A double-blind, randomized, placebo-controlled dose-ranging study to evaluate the efficacy of alosetron in the treatment of irritable bowel syndrome*, 14 ALIMENTARY PHARMACOLOGY & THERAPEUTICS, 23 (2000) (attached as Exhibit 2).

[3] Keith B. Holten & Laurie Bankston, *Diagnosing the Patient with Abdominal Pain and Altered Bowel Habits: Is It Irritable Bowel Syndrome?*, 67(10) AMERICAN FAMILY PHYSICIAN, 2157 (May 15, 2003), *available at* http://www.aafp.org/afp/2003/0515/p2157.html (attached as Exhibit 3).

[4] Douglas A. Drossman et al., *International survey of patients with IBS: symptom features and their severity, health status, treatments, and risk taking to achieve clinical benefit*, 43(6) J. CLIN. GASTROENTEROL., 541 (July 2009) (attached as Exhibit 4).

[5] Pierre Paré et al., *Health-related quality of life, work productivity, and health care resource utilization of subjects with irritable bowel syndrome: Baseline results from LOGIC (longitudinal outcomes study of gastrointestinal symptoms in Canada), a naturalistic study*, 28(10) CLINICAL THERAPEUTICS, 1726 (October 2006), *available at* http://www.sciencedirect.com/science/article/pii/S0149291806002505 (attached as Exhibit 5).

B. Lotronex Approval and the Risk Management Plan

Lotronex® (alosetron hydrochloride), a selective 5-HT3 antagonist, was approved by the Food and Drug Administration (FDA) on February 9, 2000, to treat IBS in women whose predominant bowel symptom is diarrhea. As the first drug approved to treat IBS, it met with strong patient demand and, within 10 months, 325,000 patients were taking Lotronex.

Soon after Lotronex was launched, FDA began to receive post-marketing reports of obstructed or ruptured bowels as a complication of severe constipation and ischemic colitis (sudden swelling/inflammation of part of the colon that occurs when there is a temporary loss of, or reduction in, blood flow to the colon). The agency held a public advisory committee meeting on June 27, 2000, to discuss these adverse events and risk-management options. On November 28, 2000, Lotronex was voluntarily withdrawn from the market while a restricted drug distribution program was developed for the product.

Lotronex's sponsor at the time, GlaxoSmithKline (GSK), devoted significant resources and effort to developing a risk management plan for Lotronex so that the product could return to the market to treat this debilitating condition while mitigating the risks through the risk management plan.[6] On June 7, 2002, after multiple discussions with FDA and a joint meeting of the Gastrointestinal Drugs Advisory Committee and the Risk Management Subcommittee of the Advisory Committee for Pharmaceutical Science, FDA approved a supplement to the New Drug Application (NDA) for Lotronex under the restricted distribution provisions in 21 C.F.R. § 314, Subpart H, permitting Lotronex to return to the market with a narrowed indication and a detailed risk management program. The risk management program was designed to decrease the risk of ischemic colitis and serious complications of constipation through the enrollment of qualified physicians into a prescribing program, an education program for physicians, pharmacists and patients about the risks and benefits of Lotronex, the collection and reporting of serious adverse events associated with the use of Lotronex, in addition to the ongoing evaluation of the effectiveness of the risk management program.

C. The Current REMS for Lotronex

On Sept 27, 2007, the Food and Drug Administration Amendments Act of 2007 (FDAAA) was signed into law. It created Section 505-1 of the FDCA, which permits FDA to require a REMS as part of an application for drug approval if the agency determines that a risk management plan "is necessary to ensure that the benefits of the drug outweigh the risks of the drug."[7] In addition, FDAAA provided that if FDA "becomes aware of new safety information" and determines that a

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[6] Risk management plans became known as RiskMAPs. RiskMAPs are the predecessor to today's REMS and were defined as "a strategic safety program designed to meet specific *goals* and *objectives* in minimizing known risks of a product while preserving its benefits." FDA, *Guidance for Industry: Development and Use of Risk Minimization Action Plans*, 5 (March 2005) (emphasis in original).

[7] 21 USC 355-1(a)(1).

REMS is necessary to ensure that the benefits outweigh the risks of the drug, FDA may require a REMS for a previously approved application.[8]

A REMS must contain a timetable for submission of assessments of the REMS, and may also include a medication guide, patient package insert, and a communication plan. In addition, FDA may require a REMS to include elements to assure safe use (ETASU), provided certain requirements are met.[9] FDA can only require ETASU as a component of a REMS if the drug is associated with a serious adverse drug experience and can be approved only if such elements are required as part of a strategy to mitigate a specific serious risk. If the drug was initially approved without ETASU, FDA must determine that the other REMS elements are not sufficient to mitigate the serious risk in order for FDA to require ETASU.[10] A REMS with ETASU may also be required to have an implementation system to assist the drug's sponsor with monitoring and evaluating the implementation of the elements by health care providers, pharmacists, and other persons responsible for implementing ETASU.[11]

FDAAA provided that if the applicable listed drug has a REMS, a generic drug referencing that listed drug must also have a REMS with certain of the same elements of the REMS approved for the applicable listed drug, including a Medication Guide and ETASU. In addition, 505-1(i)(1) of the FDCA provides that "a drug that is the subject of an [ANDA] and the listed drug shall use a single, shared system. . . ."[12] The statute provides that the single shared REMS requirement can be waived if FDA determines that "the burden of creating a single, shared system outweighs the benefit of a single, [shared] system, taking into consideration the impact on health care providers, patients, the applicant for the abbreviated new drug application, and the holder of the reference drug product."[13]

FDAAA provided that drugs with certain risk management plans agreed to or required by the agency prior to the passage of FDAAA were deemed to have REMS, and sponsors of those drugs were required to submit a REMS for review and approval by the agency.[14] Based on the risk management plan in place at the time FDAAA was enacted, Lotronex was deemed to have a REMS. Prometheus, having acquired Lotronex from GSK on October 31, 2007, submitted a REMS for Lotronex. On September 2, 2010, the Lotronex REMS was approved.

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8 21 USC 355-1(a)(2).

9 21 USC 355-1(d), (e), (f).

10 21 USC 355-1(f)(1).

11 21 USC 355-1(f)(4).

12 21 USC 355-1(i)(1)(B).

13 21 USC 355-1(i)(1)(B)(i).

14 FDAAA § 909(b)(2).

The current REMS is referred to as the Prescribing Program for Lotronex (PPL). The PPL has four main components in addition to a Medication Guide: (1) healthcare provider certification consisting of education and enrollment; (2) patient education; (3) pharmacy distribution only to patients with documentation of safe use conditions; and (4) an implementation system to monitor compliance. All components of the REMS work together and are necessary for the safe use of Lotronex. The components of the PPL are described in more detail below.

1. Prescriber Enrollment and Education

Only licensed healthcare providers may enroll in the PPL. The REMS provides that only prescribers who are enrolled in the PPL can prescribe Lotronex. Once a prescriber's enrollment is approved by Prometheus, he or she is entered into a database as a certified enrolled prescriber. Prometheus provides educational materials and product-safety information to enrolled prescribers, including a PPL-kit overview letter, Patient Acknowledgment Forms, Medication Guides, PPL prescription stickers, and a patient follow-up survey. Additional prescriber education information is also available on the Lotronex PPL website.[15] This enrollment process ensures that all healthcare providers who prescribe Lotronex fully understand the risks associated with improper use of the drug and educate patients on how to safely use it.

2. Patient Education and Acknowledgement

Patients may only be prescribed Lotronex after being educated on the safe use of the drug. Patient education ensures that patients understand the risks associated with Lotronex and how to safely use the drug.

3. Pharmacy Distribution

Pharmacists are provided with educational materials concerning Lotronex and proper procedures to ensure that its distribution is consistent with the PPL, including that the prescription was written by a certified and enrolled prescriber. Also, pharmacists are required to ensure that all prescriptions are accompanied by a Medication Guide.

4. Program Monitoring

Prometheus closely monitors compliance with the PPL and undertakes considerable outreach to ensure healthcare providers understand the parameters of the REMS and how to safely use Lotronex. For example, Prometheus conducts surveys of pharmacists, prescribers, and patients to help ensure that Lotronex prescriptions are written by certified enrolled prescribers and dispensed by pharmacists in accordance with PPL requirements. Patients can pre-enroll in the survey by completing a form provided by their prescriber. If any of the elements of the PPL are

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[15] *See* Lotronex, *Welcome to Prescribing Program for Lotronex (PPL), available at* http://www.lotronexppl.com (attached as Exhibit 6).

found to be inadequate, Prometheus takes reasonable steps to improve its implementation and address noncompliance. Prometheus provided REMS assessments to FDA every 6 months for the PPL's first year of implementation, and has provided assessments annually for every year thereafter.

D. Roxane ANDA for Alosetron Hydrochloride

Roxane Laboratories, Inc. (Roxane) has submitted an Abbreviated New Drug Application (ANDA) for a generic form of Lotronex. In January 2011, after receiving a Paragraph IV certification from Roxane regarding its ANDA, Prometheus filed suit against Roxane in the United States District Court, District of New Jersey, alleging infringement of a method of treatment patent that protects the use of Lotronex according to the label as set forth in United States Patent 6,284,770.

Since filing suit against Roxane, Prometheus was allowed to amend its complaint to add the active pharmaceutical ingredient (API) manufacturer, Cipla, Ltd. (Cipla). All discovery has ended in the case. A Markman hearing was held in October 2012, but no decision has been rendered to date. There is also a summary judgment motion pending which was filed by Cipla and Roxane. No trial date has been set.

Prometheus has begun discussions with Roxane over developing a single shared REMS system that would apply to both Lotronex and Roxane's generic form of Lotronex, but, to date, has not reached any agreements with Roxane regarding the nature of a single shared REMS. In fact, it was our attempt to understand and address all of the issues we raise in this petition that led us to the conclusion that the unresolved issues raised by single shared REMS are so difficult and important that notice and comment rulemaking is both necessary and appropriate.

II. ARGUMENT

A. FDA Should Provide Standards and Processes for the Development of Single Shared REMS and Waivers from the Requirement for a Shared REMS through Notice and Comment Rulemaking

Under Section 505-1 of the FDCA, "a drug that is the subject of an [ANDA] and the listed drug shall use a single, shared system under subjection (f)."[16] The statute also provides that the single shared REMS requirement can be waived for an ANDA and the ANDA applicant permitted "to use a different, comparable aspect of the elements to assure safe use" if FDA determines that:

1) the burden of creating a single, shared system outweighs the benefit of a single, [shared] system, taking into consideration the impact on health care

[16] 21 USC 355-1(i)(1)(B).

providers, patients, the applicant for the abbreviated new drug application, and the holder of the reference drug product; or

2) 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.[17]

Finally, the FDCA 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 an application under section [505](b)(2) or (j) or to prevent application of such element under subsection (i)(1)(B) to a drug that is the subject of an [ANDA]."[18]

While the statute does not define what is meant by a single shared REMS, one possible interpretation of this provision is that that the innovator and a generic competitor must negotiate and enter into a contract to work together to provide competing drugs to the marketplace. This requirement is unprecedented among federal laws and, to our knowledge, no other federal law requires one party to negotiate, and reach an agreement with, a specific identified competitor and work together as business partners for the foreseeable future.[19]

1. FDA Has Issued No Meaningful Guidance Regarding Single Shared REMS or Waivers from the Requirement for a Shared REMS

Despite the unprecedented nature of the single shared REMS requirement, FDA has not provided any meaningful guidance on single shared REMS or waivers from the requirement for a single shared REMS in the five years since FDAAA was enacted.[20]

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17 21 USC 355-1(i)(1)(B)(i)-(ii).

18 21 USC 355-1(f)(8).

19 Indeed, the closest analogy is the Federal Trade Commission's (FTC's) authority under § 7 of the Clayton Act and § 5 of the Federal Trade Commission Act, which permits the agency to order a divestiture of assets to counter the potential or realized anti-competitive effects of a merger. *See* 15 USC §§ 18, 45. The FTC or Department of Justice (DOJ) may require divestiture of certain assets prior to permitting a merger. However, divestiture is a willful, prospective action – the parties wish to enter into a merger, and divesting of assets is necessary to correct any anti-competitive effects of the desired merger and conform it to the requirements of the law. If a party does not want to divest, it may bow out of the proposed merger.

20 FDA has issued a draft guidance document regarding REMS, but while the guidance document reiterates the statutory requirement for a single shared REMS, it offers no meaningful guidance on shared REMS. *See* FDA, *Draft Guidance for Industry: Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications* (September 2009). The agency also convened a public meeting to discuss REMS, including single shared REMS, in June 2010, but, even at that meeting, FDA did not offer any insights into its current thinking regarding single shared REMS.

- The term "single, shared system" is undefined in the statute and FDA has provided no parameters on what aspects of the REMS, its implementation, or assessment, must be shared to qualify as a "single shared system" under the statute.

- There is no clarity around how or when an innovator company is notified when there is an ANDA applicant such that the innovator should enter into negotiations with the ANDA applicant. Should the negotiations happen in parallel with the review process, or upon the ANDA applicant securing tentative or final approval? It will take considerable resources to design and negotiate a single shared REMS, resources that may be wasted if the ANDA cannot be approved because of deficiencies in the application or manufacturing process.

- There is no guidance on how the innovator company and the ANDA applicant are to navigate the sensitive issues around negotiating an agreement when the parties are opposite each other in Hatch-Waxman litigation, including whether negotiations should occur in parallel with the litigation, or after the litigation, or 30-month stay, has concluded, or upon tentative or final approval.

- FDA has not offered guidance on how sponsors must share costs and responsibilities under a single shared REMS.

- FDA has provided no guidance on how adverse events should be collected and provided to the agency from a single shared REMS.

- FDA has provided no direction as to how to modify a single shared REMS, should the sponsors disagree on changes to the REMS or how future safety concerns should be addressed by a revised REMS.

- FDA has provided no guidance on how a single shared REMS must be further revised as additional generic companies seek approval.

- FDA has not provided any explanation of the process or standards for granting a waiver to a generic company from the requirement of a single shared system.

- FDA has offered no guidance on the factors that may lead to a determination that ETASU are being used to block or delay approval of an ANDA or 505(b)(2) NDA or the consequences of such a determination.

FDA's failure to provide meaningful direction to industry regarding single shared REMS or the process and standards for granting a waiver from the requirement for a single shared REMS, and the industry's uncertainty around key issues with single shared REMS, has likely contributed to the scarcity of single shared REMS approved under 505-1 of the FDCA.

2. Single Shared REMS Precedent is Limited

To date, more than five years after the enactment of FDAAA, there is very little publicly available information to guide sponsors attempting to negotiate a shared REMS with their competitor. Over 65 drugs are approved by FDA with individual REMS, approximately twenty-five of which have ETASU as components of the REMS. Only six of these REMS with ETASU operate under a single shared REMS.[21] None of the shared REMS appear to have been negotiated and finalized against the backdrop of patent litigation between the parties.

The Rosiglitazone REMS appears to be one of the few single shared REMS adopted pursuant to the 505-1(i) requirement that an innovator and generic use a single shared system. A review of the publicly available information gives no guidance as to how the parties are sharing costs and responsibilities or how the REMS will be modified in the future to address new or different risks or changes in the sponsors with approved applications.

The recently approved REMS for the generic buprenorphine products for opioid dependence treatment appears to be the first and only time that FDA has waived the requirement that a generic use a single shared REMS with the listed drug referenced by the generic. Public notice of the waiver consisted of a footnote in a response to a citizen petition filed by the innovator on issues unrelated to the REMS in which FDA stated that it had waived the requirement that generics use a single shared system with the listed drugs. FDA explained "[t]his waiver was granted because FDA determined that the statutory criteria in Section 505-1(i) of the FD&C Act were met. When a waiver is granted, ANDAs may be subject to different but comparable aspects of the ETASU for the RLDs [reference listed drug]."[22] There is no explanation of how FDA determined the criteria were met, and no indication of the process used to reach that determination, including whether the parties had an opportunity to participate in the process. Thus, there is nothing to inform parties currently negotiating shared REMS as to when a potential waiver may be under consideration by the Agency, how the parties may participate in that process, or how FDA weighs and adjudicates the waiver criteria in the statute.

The other shared REMS appear to be class-based REMS where the program participants voluntarily developed the singled shared REMS for drug products that were already on the market.[23] Many of the products had been distributed with some sort of a risk management

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[21] According to FDA's publicly available list of approve REMS, shared REMS have been approved for the following classes of drugs: isotretinoin, transmucosal immediate-release fentanyl, extended release/long acting opioid analgesics, mycophenolate, rosiglitazone, and buprenorphine for opioid dependence. *See* FDA, *Approved Risk Evaluation and Mitigation Strategies (REMS), available at* http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm.

[22] *See* February 22, 2013 FDA response to the Citizen Petition filed by Reckitt Benkiser (FDA-2012-P-1028), n. 45 (attached as Exhibit 7).

[23] FDAAA did not provide FDA with the authority to require a single shared REMS for classes of drugs involving more than one innovator. The statute only provided for shared REMS in the limited circumstances set out in 21 USC 355-1(i).

program before the single shared REMS. These precedents do not rely on the particular statutory provision at issue here and the publicly available documents do not provide guidance for determining how to share a REMS between an innovator company and the generic applicant that relies on that innovator product as the reference listed drug, particularly when the parties are in Hatch-Waxman litigation.

3. FDA Should Provide Direction and Standards for Single Shared REMS Through Notice and Comment Rulemaking; Without a Final Rule, Innovator Companies Face Increased Scrutiny and Uncertain Antitrust and Product Liability Risks

A central tenet of the Administrative Procedure Act (APA) is that agency rules established through notice and comment rulemaking provide clarity to the parties involved and the agencies and courts enforcing the rules, resulting in more consistency in the actions of regulated industry and the responsible regulatory agencies. Notice-and-comment rulemaking procedures allow "the agency to benefit from the experience and input of the parties who file comments," "encourages public participation in the administrative process," and "educates the agency, thereby helping to ensure informed agency decisionmaking."[24]

FDA has recognized that developing a single shared REMS may be difficult and that input from affected parties is important to the agency's understanding of the issues. In a 2009 notice of a public meeting on REMS for certain opioid drugs, FDA asked participants to answer "What obstacles need to be addressed before such a system could be developed?"[25] Presumably FDA has received valuable information and insight, but none of that information or insight has been passed on to regulated industry faced with the expectation that it design and negotiate a single shared REMS with its competitor.

Rulemaking not only delivers higher quality guidance and standards on key regulatory issues, but also makes more efficient use of agency and industry resources by establishing a shared understanding of substance and process. This eliminates the need for agencies and affected parties to engage in expensive and time-consuming one-off adjudications over recurring issues. FDA's own regulations recognize that the agency "may propose and promulgate regulations for the efficient enforcement of the laws administered by FDA whenever it is necessary or appropriate to do so."[26] The statutory creation of single shared REMS represents a significant change in law, and is clearly an appropriate and necessary cause for new rulemaking.

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[24] Chocolate Mfrs. Ass'n of U.S. v. Block, 755 F.2d 1098, 1103 (4th Cir. 1985).

[25] FDA, *Risk Evaluation and Mitigation Strategies for Certain Opioid Drugs; Notice of Public Meeting*, 74 Fed. Reg. 17967, 17970 (Apr. 20, 2009).

[26] 21 CFR 10.40(a); *see also* 21 USC 371(a).

Engaging in rulemaking will not only fulfill the directives created by FDAAA to ensure that REMS are not unduly burdensome on patients and the healthcare delivery system, but will also help ensure the prompt and efficient review, approval, and marketing of ANDAs.[27] Without FDA guidance on the standards applicable to single shared REMS, it is possible the agreements reached by the innovator company and ANDA applicant could place an undue burden on patients or the healthcare delivery system. Moreover, without direction and clear standards to the affected sponsors regarding single shared REMS, the agency would likely need to engage in negotiations and discussions over each single shared REMS or waiver, wasting valuable agency resources and delaying the ultimate approval and marketing of ANDA products. Furthermore, without any guidance, standards, or clear expectations from the agency, sponsors must devote significantly more resources and time to developing and negotiating single shared REMS. This unnecessary use of resources and time benefits no one; not the patients, not the healthcare system, not the agency and certainly not the sponsors.[28]

FDA rulemaking will offer crucial direction on standards and processes to parties, like Prometheus, who are attempting to reach agreement with potential generic entrants in ways that ensure the safe use of the drugs, comply with agency expectations and protect the parties from undue risks. With no standards or guidance and no useful precedent, sponsors face significant resource commitments, as well as uncertain risks arising from antitrust law and product liability, as they enter into negotiations and attempt to finalize agreements with ANDA applicants to share REMS.

Prometheus understands the REMS statute is structured to deliver single shared REMS, including an innovator company and the generic company that references that innovator company's products, and so we have engaged in good faith discussions with Roxane and have attempted to understand and minimize any undue risks arising from antitrust law and product

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[27] *See* 21 USC 355-1(f)(2), (5) (requiring that a REMS' elements to assure safe use are not "unduly burdensome on patient access" and "to the extent practicable, [] minimize the burden on the health care delivery system" and directing the Secretary to "evaluate," "assess," and "seek input" on the elements to assure safe use and provide guidance to ensure that they are not unduly burdensome).

[28] Indeed, it is not just Prometheus that believes guidance and standards are necessary for single shared REMS. There are a number of citizen petitions and comments to guidance pending with FDA raising similar or related issues. *See, e.g.*, the February 2010 Citizen Petition filed by Roxane (FDA-2010-P-0076) requesting FDA ensure that generic companies have a role in developing and implementing REMS and that innovators do not impose unreasonable financial burdens on generic companies that are required to participate in a REMS; *see also* the June 2009 Citizen Petition filed by Dr. Reddy's Laboratories, Inc. (FDA-2009-P-0266) requesting FDA enforce the FDCA provision prohibiting innovator companies from using a REMS to block or delay generic competition, and refer complaints from generic companies alleging that innovator companies are using REMS to block or delay generic competition to the FTC. In addition, innovator companies have expressed confusion regarding the timing of when negotiations with ANDA sponsors should occur. *See, e.g.,* the July 2012 Citizen Petition filed by Jazz Pharmaceuticals, Inc. (FDA-2012-P-0773) requesting FDA not to accept for review any ANDA referencing a RLD with a risk management system that does not contain, at the time of its submission, a proposed risk management system, and FDA's response noting that such a requirement could delay generic approval, and that the agency would generally instruct ANDA applicants to work with RLD sponsors to negotiate single shared systems subsequent to ANDA submission. (Attached as Exhibit 8).

liability. However, we also are very aware and concerned that any agreement reached with our primary competitor that may serve as the gateway to that competitor entering the market will be scrutinized by the Federal Trade Commission (FTC) for antitrust issues and likely the plaintiff's bar in the context of product liability litigation.

a. Possible Scrutiny With Respect To Antitrust Issues

The pharmaceutical industry has been a primary target of antitrust scrutiny by the FTC and the courts. FTC has particularly focused on agreements between innovator and generic companies that allegedly have the effect of delaying generic entry; these often arise in connection with settling patent litigation. In this context, an innovator company that is required to share its REMS with an ANDA applicant – possibly conveying significant value to the ANDA filer – must navigate significant potential antitrust concerns. These concerns can arise, on one hand, if the innovator company reaches an agreement with the generic company regarding the single shared REMS program or, on the other, if the parties reach an impasse and cannot agree on a shared program. Either way, the absence of clear guidance and standards from FDA increases the antitrust uncertainty and forces the innovator company into an unnatural negotiation that is fraught with antitrust risk.

Since the 1990s, a major target of FTC antitrust enforcement has been patent litigation settlements between innovator and generic companies that involve the innovator company providing some form of consideration to the generic company, with the generic company agreeing not to enter the market prior to a certain date.[29] FTC theorizes that, absent such consideration, the parties would have negotiated an earlier entry date for the generic drug product, and therefore the consideration is a "reverse payment" or a "payment for delay," and is presumptively illegal. According to the FTC, the consideration need not be an actual cash payment – the consideration could be disguised if the innovator company "overpays" the generic company for services or assets it receives from the generic company,[30] or it may not involve a payment at all, such as a promise by the innovator company not to launch an authorized generic.[31] Because of this concern, Congress has required that all agreements between innovator companies and ANDA applicants regarding "the manufacture, marketing, or sale" of the ANDA

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[29] *See* Prepared statement of the Federal Trade Commission before the Subcommittee on Commerce, Trade, and Consumer Protection, Committee on Energy and Commerce, United States House of Representatives, *Protecting Consumer Access to Generic Drugs: The Benefits of a Legislative Solution to Anticompetitive Patent Settlements in the Pharmaceutical Industry* (May 2, 2007) (attached as Exhibit 9).

[30] *See* Schering Plough Corp et al. v. Federal Trade Comm'n, 402 F.3d 1056 (11th Cir. 2005) (FTC alleged that the $60 million payment made by Schering to Upsher was not a bona fide royalty payment for certain Upsher products).

[31] Brief for the Federal Trade Commission Brief as Amicus Curiae, In re: Effexor XR Antitrust Litigation, Case No. 3:11-cv-05479 (D.N.J), filed August 10, 2012, *available at* http://www.ftc.gov/os/2012/08/120810effexoramicusbrief.pdf (attached as Exhibit 10).

product that are reached during the pendency of Hatch-Waxman litigation be submitted to the FTC and Department of Justice for review.[32]

Against this backdrop, FDA is requiring innovator companies and ANDA applicants to work together on developing single shared REMS, even though such companies have received no direction from FDA on how to approach single shared REMS negotiations, and may be locked in active patent litigation. Importantly, there is a good chance that the generic company seeking to enter the market will have filed a Paragraph IV certification and be actively litigating the patents at the same time that it is seeking REMS access. Just as likely, the parties will be exploring ways to settle the patent litigation, potentially with a compromise entry date.

Many REMS programs require a substantial investment of resources by the innovator company, and presumably the parties will need to reach an agreement concerning how much the ANDA applicant should pay the innovator company for its past investment, as well as ongoing costs in the future to keep the program functioning. Because this negotiation is compelled by statute and not an ordinary marketplace negotiation, there is no market-based mechanism to assist in determining an appropriate level of compensation to the innovator company, and what other terms would be appropriate for such an agreement. Indeed, this is precisely why courts are very reluctant to force companies to deal with their competitors.[33] Without further direction from FDA regarding the scope and nature of an acceptable program, the parties run the risk that an agreement that is undertaken in connection with, or even just contemporaneous to a patent litigation settlement, may be challenged by the FTC or others as a "reverse payment" that is presumptively illegal.

Conversely, the innovator company and ANDA applicant may have very different views concerning the scope of an appropriate REMS program, or may be unsuccessful in reaching an agreement regarding how the costs and responsibilities of the program should be allocated between them. As a result, the generic drug product's entry into the marketplace may be delayed by its failure to have an approved REMS. In such circumstances – even if the innovator company in good faith believes that the business terms it is requesting in return for access to the REMS are reasonable, and/or that acceding to the generic company's demands will result in overcompensation to the generic company – there is a risk that the innovator company may be accused of violating FDCA 505-1(f)(8) by allegedly using its REMS program to block or delay

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[32] Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA), § 1112(a). The agreements are required to be filed not later than 10 business days after the agreements are executed. Failure to timely file these agreements may result in a civil penalty of $11,000 for each day the filing is late. MMA §§ 1113, 1115.

[33] *See* Verizon Commc'ns Inc. v. Law Offices of Curtis V. Trinko, 540 U.S. 398 (2004). The Supreme Court declined to require that a monopolist deal with its rivals, noting that "[e]nforced sharing also requires antitrust courts to act as central planners, identifying the proper price, quantity, and other terms of dealing – a role for which they are ill-suited. Moreover, compelling negotiation between competitors may facilitate the supreme evil of antitrust: collusion." *Id.* at 408.

the approval of the generic applicant.[34] Additionally, the innovator company's refusal to come to terms with the ANDA applicant may be challenged as an abuse of the FDA regulatory scheme to maintain a monopoly in violation of Section 2 of the Sherman Act.[35] Here, again, the lack of FDA standards exposes the innovator company to legal challenge.

A rulemaking by FDA providing clear direction on what must be included in single shared REMS and how the innovator and generic companies must interact in the development, implementation, and maintenance of single shared REMS is needed to assure innovator companies that they can comply with the single shared REMS requirement without undue antitrust risk.

b. Possible Scrutiny In the Context of Product Liability

In addition, innovator companies are being directed, without any guidance or established standards from the agency, to share a single REMS with a generic company in the face of uncertainty around the dual-liability system created by the Supreme Court's recent rulings in *Pliva v. Mensing* and *Wyeth v. Levine* and potential liability imposed upon innovator companies for injuries allegedly caused by generic competitors.[36] As was made clear by the *Pliva* and *Wyeth* rulings, under the FDCA and its implementing regulations, the innovator company has control over a product's label, including adding or updating risk information. The REMS and all of the labeling that is required for the REMS to work, such as educational material and enrollments forms, are reviewed and approved by the agency just like a product's label and can only be changed after submission and approval of a supplement to the application.[37] Under *Wyeth*, an innovator company can be sued and held liable for a failure to warn if the drug's label is not updated to reflect new safety or risk information.[38] However, in *Pliva,* the Court reached

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[34] In fact, we note that FDA referred to comments filed in response to a citizen petition that claimed that the innovator was attempting to delay approval of generic products through its lack of cooperation with the efforts of FDA and the generics to negotiate a shared REMS and stated that it was referring the matter to FTC, noting that FTC has the expertise to investigate and address anticompetitive business practices. February 22, 2013 FDA response to the Citizen Petition filed by Reckitt Benkiser (FDA-2012-P-1028) (attached as Exhibit 11).

[35] *Cf.* In the Matter of Bristol-Myers Squibb Co., Complaint, Dkt. No. C-4076 (Fed. Trade Comm'n April 18, 2003*), available at* http://www.ftc.gov/os/caselist/c4076.shtm (alleging that Bristol-Myers Squibb's provided FDA with false and misleading *Orange Book* patent listing information, which constitutes illegal monopolization) (attached as Exhibit 12).

[36] *See, e.g.,* Pliva, Inc. v. Mensing, 131 S. Ct. 2567 (2011); Wyeth v. Levine, 555 U.S. 555 (2009).

[37] The REMS Guidance states that modifications to REMS are submitted as prior approval supplements. FDA, *Draft Guidance for Industry: Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications*, 23 (September 2009). We recognize that the recently enacted Food and Drug Administration Safety and Innovation Act (FDASIA) will permit the agency to issue guidance describing minor changes to a REMS that will not require a prior approval supplement and changes to a REMS that can be made after notification of the agency: the provisions, however, do not change the fact that many of the pieces of a REMS constitute labeling under the FDCA.

[38] Wyeth v. Levine, 555 U.S. 555 (2009).

the opposite conclusion for a generic company – because the generic company has little control over the content of its label, it cannot be held liable for failing to warn patients.[39]

The perceived unfairness created by the dual liability system, however, has caused at least a few courts to abandon the traditional product liability concepts to allow injured plaintiffs who ingested a generic product to recover from the brand manufacturer. For example, in the recent decision of *Weeks v. Wyeth*,[40] the Supreme Court of Alabama held that under Alabama law, defective labeling of a brand-name prescription drug manufacturer's product may render that manufacturer liable for fraud or misrepresentation for injuries caused by their competitors' generic products. This ruling abandons the traditional notion of product liability law, which requires that an injured plaintiff actually consume, ingest or be exposed to a product manufactured by the defendant for the plaintiff to recover. Rejecting the majority approach in almost all other states, with *Weeks*, Alabama joins Vermont and California[41] as three states that have endorsed this type of "innovator liability." While Alabama, Vermont and California hold the minority view, the majority of courts that have held that innovator manufacturers should not be held liable for alleged injuries caused by their generic competitor's products have done so before the *Pliva* ruling in 2011 (which arguably leaves a plaintiff injured by a generic with no recourse for a failure to warn claim). It remains to be seen whether other courts are swayed in a different direction, as the Alabama Supreme Court was, by the new landscape created by *Pliva*.

It is not clear how this complicated liability analysis would be applied to generic products distributed under a single shared REMS. For instance, if a single shared REMS provides for each sponsor to implement the REMS' ETASU when its own product is prescribed and dispensed, would a patient who was injured by the generic product be without recourse under *Pliva,* or would the court determine that, because the innovator company permitted the generic company to share the REMS through independent implementation of the ETASU, the innovator company should be held liable for injuries caused by the generic product?

To date, sponsors have been given no guidance or standards as to how a single shared REMS should be designed or modified after approval. It is unclear if any agreement reached between an innovator and a generic company as to the REMS will be subject to state court review in determining liability in a state tort failure to warn case. In the face of this uncertainty, FDA must provide guidance and standards around these issues before single shared REMS are negotiated, as it is likely that REMS will be the subject of future litigation in failure to warn cases.

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39 Pliva, Inc. v. Mensing, 131 S. Ct. 2567 (2011).

40 Wyeth v. Weeks, WL 13573 (Ala. 2013).

41 Kellogg v. Wyeth, 762 F. Supp 2d 694, 709 (D. Vt. 2010) (finding that "brand-name manufacturer owes a duty to use reasonable care to avoid causing injuries to consumers of the generic bioequivalents of its drugs."); Conte v. Wyeth, 168 Cal. App. 4th 89 (2008) (the Court explained that a duty exists because the brand name manufacturer "knew or should have known" that a significant number of patients whose doctors rely on brand name product information are likely to have generic drugs prescribed or dispensed to their patients.). (Attached as Exhibit 13).

c. Agreements that Protect Innovator Companies Against These Risks May be Unpalatable to ANDA Applicants

Finally, we note that any agreement to share a REMS that offers protection against these uncertain risks may be unpalatable to ANDA applicants, who typically make relatively low investments to enter the market. ANDA applicants may assert that attempts by the innovator company to negotiate such issues as part of a single shared REMS agreement are designed to delay the marketing of their ANDA. FDA's failure to provide clarity on the difficult issues regarding single shared REMS puts innovator companies in the untenable position of structuring an agreement to manage product liability risks as well as antitrust risks, while faced with the threat that failure to reach an agreement with the ANDA applicant may be viewed as blocking or delaying approval.

An innovator company's position is made even more precarious without clear standards or process governing a waiver from the requirement of a single shared REMS. Without understanding the conditions under which FDA believes a waiver would be appropriate, the process for requesting a waiver, or the process FDA will follow in responding to a waiver request, including whether an innovator company will have any notice of or opportunity to weigh in on a pending waiver request, innovator companies cannot appropriately balance the burden of operating under a single shared REMS with the possibility that FDA will waive the single shared REMS requirement and permit the ANDA applicant to operate its own, comparable REMS.

4. FDA Must Give Sponsors Notice and an Opportunity to Participate in the Process of Evaluating a Waiver Request

As discussed above, the statute provides that the single shared REMS requirement can be waived and an ANDA applicant permitted to use a different, comparable aspect of the elements to assure safe use required of the innovator if FDA determines that:

> the burden of creating a single, shared system outweighs the benefit of a single, [shared] system, taking into consideration the impact on health care providers, patients, the applicant for the abbreviated new drug application, and the holder of the reference drug product. . .[42]

The statute explicitly requires FDA to consider the impact a waiver from the requirement for a shared REMS has on the holder of the reference product. Such information is not readily available to FDA. Thus, FDA must seek input from the sponsor of the reference product to fulfill its statutory obligation to weigh the burden of a shared REMS against the benefit of a shared REMS as only the sponsor of the reference product can accurately inform the agency the impact a waiver will have on it.

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[42] 21 USC 355-1(i)(1)(B)(i).

In addition, given that it is the sponsor of the reference drug that will likely have had years of experience in administering the REMS, giving the sponsor extensive opportunity to interact with healthcare providers and patients regarding the REMS, the sponsor of the reference drug product is likely to have important information and unique insight into the impact a waiver of the shared REMS will have on healthcare providers and patients. Accordingly, FDA cannot properly make a determination on a waiver request without the input of the sponsor of the reference drug product. Indeed, such a conclusion is reflected in the statutory requirement that FDA specifically consider the impact on the innovator of a waiver from the requirement of a shared REMS.

Furthermore, FDA must provide notice to the sponsor of the reference product when a waiver has been requested. First, such notice is necessary to permit the sponsor of the reference product to provide FDA with information on the impact a waiver might have. Second, without knowledge that a waiver request is pending, or an understanding that it will be notified if a waiver request is made, an innovator is hampered in its ability to negotiate a shared REMS with an ANDA sponsor as the innovator will not know whether the ANDA sponsor is negotiating in good faith or simply attempting to gather commercially sensitive information and build a record to support a waiver request.

III. CONCLUSION

The design and implementation of a REMS to mitigate the specific risks of a drug without unduly burdening the healthcare system raise some of the most complex and difficult issues facing an NDA sponsor. Requiring that sponsor to then negotiate and design a single shared REMS with its competitor, often while engaged in patent litigation, without any benefit of clear standards from FDA, forces the sponsor to expend significant resources and exposes the sponsor to uncertain, but potentially significant risks. As FDA knows well, the purpose of notice and comment rulemaking under the APA is to provide exactly the type of direction on standards and process that the parties to a potential single shared REMS need to navigate the relevant statutory provisions, while protecting the public health and minimizing the burden on the healthcare system and the sponsors. Accordingly, FDA should engage in and complete notice and comment rulemaking to clarify the procedural and substantive standards for single shared REMS and waivers of the requirement for single shared REMS. Furthermore, FDA must give an innovator notice that a waiver request has been filed and an opportunity to participate in the process of determining whether to grant a waiver from the requirement of a shared REMS.

ENVIRONMENTAL IMPACT

I. The actions requested in this petition are subject to categorical exclusions under 21 C.F.R. § 25.31.

ECONOMIC IMPACT

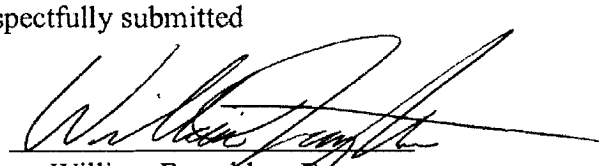
I. Pursuant to 21 C.F.R. § 10.30(b), an economic impact statement will be submitted upon request of the Commissioner.

CERTIFICATE

I. The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: February 22, 2012. I f I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Prometheus Laboratories Inc. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted

By: 

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