IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

PROMETHEUS LABORATORIES INC.
9410 Carroll Park Drive
San Diego, CA, 92121,

Plaintiff,

v.

Civil Action No. _____

SYLVIA MATHEWS BURWELL, in her official capacity as SECRETARY, UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES,
200 Independence Avenue, S.W.
Washington, DC 20201,

and

STEPHEN OSTROFF, M.D.,
in his official capacity as ACTING COMMISSIONER OF FOOD AND DRUGS,
FOOD AND DRUG ADMINISTRATION,
10903 New Hampshire Avenue,
Silver Spring, MD 20993,

Defendants.

VERIFIED COMPLAINT FOR DECLARATORY, INJUNCTIVE, AND OTHER RELIEF

Plaintiff Prometheus Laboratories Inc. ("Prometheus") hereby brings this Verified Complaint against Defendants Sylvia Mathews Burwell, solely in her official capacity as Secretary of the Department of Health and Human Services ("HHS"), and Steven Ostroff, M.D., solely in his official

capacity as Acting Commissioner of Food and Drugs, head of the Food and Drug Administration ("FDA" or the "agency"), and alleges as follows:

INTRODUCTION

1. This is an action to hold unlawful and set aside FDA's decision on May 4, 2015 to grant final approval to an application submitted by Roxane Laboratories, Inc. ("Roxane") under Section 505(j)(1) of the Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 355(j)(1), paving the way for Roxane to market a purported generic version of Prometheus' LOTRONEX® (alosetron hydrochloride) tablet.

2. Prometheus' LOTRONEX® is an FDA-approved drug used to treat severe Irritable Bowel Syndrome ("IBS") in women whose predominant bowel symptom is diarrhea. As the first drug approved to treat IBS-D, LOTRONEX met strong patient demand upon entry into the marketplace and has provided important benefits to patients. It also presents some risks, however. Specifically, there have been post-marketing reports of obstructed or ruptured bowels as a complication of severe constipation and ischemic colitis. As a result, LOTRONEX® was removed from the market and later reintroduced with FDA-required restrictions on its distribution to mitigate the risks of the product. LOTRONEX® is now subject to a Risk Evaluation and Mitigation Strategy ("REMS"), which is a set of requirements on the distribution and marketing of a product tailored to the specific risks of a drug determined by FDA to be necessary to ensure the benefits of the drug outweigh its risks.

3. The FDCA expressly mandates that, before a generic version of a drug subject to a REMS like that imposed on LOTRONEX® is approved, FDA must require the generic drug to use a single, shared REMS with the reference drug, unless the generic applicant qualifies for a statutory

waiver. The statute does not contemplate the attachment of any qualifications or conditions upon the waiver: either a generic drug qualifies for a waiver or it does not. 21 U.S.C. § 355-1(i)(1)(B). In approving Roxane's generic version of LOTRONEX®, however, FDA granted a waiver of the statutorily required single, shared REMS that was subject to Roxane meeting two conditions. Because the statute does not contemplate attaching qualifications or conditions to the waiver, FDA's conduct is unlawful, arbitrary and capricious and otherwise violates the Administrative Procedure Act ("APA"). In addition, FDA's grant of a waiver also was unlawful, arbitrary and capricious because it failed to meet the statutory requirements for a waiver.

4. FDA's actions pose a substantial and imminent harm to patients. By creating two distinct REMS programs, FDA has increased and complicated the compliance obligations imposed on prescribers and pharmacists, which almost certainly will increase the occurrence of prescribing and dispensing errors and undermine the clarity and quality of the communications from prescribers and pharmacists that FDA has determined patients need to assure the safe use of alosetron hydrocholoride. The risks associated with alosetron hydrocholoride are serious; for certain patients, they are significant. The REMS imposed by FDA is intended to limit the drug's use to those patients for whom the benefits outweigh the risks. By approving a separate REMS for the Roxane product, FDA has created a risk of confusion or error that can result in the wrong patient taking alosetron hydrochloride, in patients not taking the drug correctly, and in patients not appropriately responding to the symptoms that can signal a serious adverse event. In addition, the heightened burdens and risks associated with multiple separate REMS could discourage treatment of the women for whom the drug is most appropriate, decrease prescriber and pharmacist compliance with any alosetron REMS, and promote

greater use of alternate medications that are not subject to the burdens of a REMS, but that are less effective or less therapeutically appropriate for this condition.

5. FDA's actions also will irreparably harm Prometheus. Upon information and belief, Roxane is poised to flood the market with its drug at any moment. Absent immediate injunctive relief, Roxane's drug will immediately overtake LOTRONEX®'s market share, drive down prices, interfere with Prometheus' ability to invest in pipeline products and support existing products, and irreparably harm both Prometheus and the public at large.

PARTIES

6. Plaintiff Prometheus Laboratories Inc. is a California company with its principal place of business at 9410 Carroll Park Drive, San Diego, CA 92121. Prometheus is a commercial-stage biotechnology company whose strategy includes the marketing and delivery of proprietary diagnostic testing services, scientific nutritional solutions and pharmaceutical products. Prometheus holds approved New Drug Application ("NDA") 021127 for LOTRONEX®.

7. Defendant Sylvia Mathews Burwell, who is being sued in her official capacity only, is the Secretary of HHS and is responsible for administering and enforcing the Food, Drug, and Cosmetic Act, 21 U.S.C. § 321, *et seq.* Defendant Burwell maintains an office at 200 Independence Avenue, S.W., Washington, D.C. 20201.

8. Defendant Stephen Ostroff, M.D., who is being sued in his official capacity only, is the Acting Commissioner of Food and Drugs and is responsible for supervising the activities of FDA, an administrative agency within HHS. Defendant Ostroff maintains offices at 10903 New Hampshire Avenue, Silver Spring, MD 20993.

JURISDICTION AND VENUE

9. Jurisdiction in this Court is grounded upon and proper under 28 U.S.C. § 1331, in that this is a civil action arising under the laws of the United States; 28 U.S.C. § 1346, in that this case involves claims against the federal government; 5 U.S.C. § 702, in that Prometheus is seeking judicial review of an agency action from which it has suffered a legal wrong, has been adversely affected, and has been aggrieved; 28 U.S.C. § 1361, in that this is an action to compel an officer of the United States to perform his or her duty; 28 U.S.C. §§ 2201-2202, in that there exists between Prometheus and the Defendants an actual, justiciable controversy as to which Prometheus requires a declaration of its rights by this Court, as well as preliminary and permanent injunctive relief to prohibit the Defendants from violating laws and regulations; and 21 U.S.C. § 355(q) and other sources of law, in that the conduct complained of constitutes final agency action.

10. Venue is proper in this Court under 28 U.S.C. §§ 1391(b) and (e) because this is a civil action in which the Defendants are officers of the United States acting in their official capacities and one of the Defendants maintains her office and conducts business in this judicial district. Moreover, a substantial part of the events giving rise to the claims herein occurred within this judicial district.

11. Prometheus has standing to bring the present lawsuit because it is suffering and faces additional actual injury as a result of FDA's decisions and because it is within the zone of interest of the relevant statutory provisions.

NATURE OF THE CASE

I. Statutory and Regulatory Background

A. New Drug Approval Process

12. The FDCA requires all new prescription drugs to obtain FDA approval before they can enter the marketplace. 21 U.S.C. § 355(a). Manufacturers of brand name ("pioneer" or "innovator" drugs) must demonstrate the safety and effectiveness of their products in order to gain FDA approval. Typically, that is done by conducting pre-clinical and clinical studies and submitting the resulting data to FDA in an NDA. 21 U.S.C. § 355(b)(1). In order to encourage the development of innovator products, the statute provides them with certain periods of regulatory exclusivity and patent-related protections that make it more difficult for certain competing products to come to market. *See generally* the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417 (Sept. 24, 1984) ("Hatch-Waxman Amendments" to the FDCA).

B. Generic Drug Approval Process

13. After those periods of protection, however, the statute provides a path for a generic version of a previously-approved innovator product (known in this context as the "reference listed drug" or "RLD") to come to market. Generic drugs are approved by means of an Abbreviated New Drug Application ("ANDA"), which contains information and data to show that the proposed generic product is the "same as" the RLD in terms of active ingredient, strength, dosage form, route of administration, and bioavailability (generally, the rate and extent to which the drug enters the bloodstream). 21 U.S.C. § 355(j)(2)(A)(iii); 21 U.S.C. § 355(j)(8)(A)(i). Based on these similarities and the proposed generic having the same labeling as the RLD (as required by the statute), approval of

an ANDA is based on FDA's concluding that its previous finding that the RLD is safe and effective is equally applicable to the generic product. 21 U.S.C. § 355(j)(2). Accordingly, the ANDA approval process allows an applicant to avoid independently demonstrating its product's safety and efficacy, and thus bring the product to market much more quickly and inexpensively.

C. Risk Evaluation And Mitigation Strategies (REMS)

14. As noted, a REMS is a set of requirements on the distribution and marketing of a product tailored to the specific risks of a drug. FDA has authority to require a REMS at the time of a new drug approval or after approval if new safety data becomes available 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." 21 U.S.C. § 355-1(a)(1). Among other things, FDA may require a REMS to include elements to assure safe use ("ETASU"), which are required to mitigate a specific and serious risk listed in the labeling of the drug. Depending on the specific risks of the drug, ETASU may include requirements that healthcare providers who prescribe the drug have particular training, experience, or are specially certified, pharmacies that dispense the drug are specially certified, and the drug be dispensed to patients with evidence or other documentation of safe-use conditions.

15. When a product is subject to a REMS that includes ETASU, a proposed generic version of that approved product is also required to be subject to a REMS with the same ETASU as the RLD. 21 U.S.C. § 355-1(i)(1)(B). Moreover, unless specific conditions are met, the generic product and the innovator product must use a single, shared REMS to mitigate the risks of both the innovator and generic products. The statute expressly states that "a drug that is the subject of an [ANDA] and the [RLD] ***shall*** use a single, shared system . . . ." *Id.* (emphasis added). The purpose of requiring a

single, shared system is to minimize the burdens on the healthcare system and therefore to maximize the protections provided by a REMS. *See* Food and Drug Administration, *FDA/CDER to Prometheus Laboratories, Inc.—Petition Denial (Docket No. FDA-2013-P-0572),* REGULATIONS.GOV (Oct. 7, 2013) at 5.

16. FDA may waive the statutory requirement for a single, shared REMS and allow the generic product to come to market with a "different, comparable aspect of the elements to assure safe use" only in two circumstances, only one of which is relevant here. A waiver is permitted if:

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

21 U.S.C. § 355-1(i)(1)(B)(i)-(ii). The second exception is not at issue in this case, but the structure and language of the statute make clear that a single, shared REMS is the norm, and approval of a separate but comparable REMS is permitted only in rare circumstances. Importantly, the FDCA does not authorize FDA to attach any qualifications or conditions to any waiver of the statutory requirement that generic drugs and the RLD share a single, shared REMS with their RLDs.

17. This is reflected in how the agency has approved generic products with REMS requirements in the more than six years the REMS framework has been effective. Although establishing a single, shared REMS can be a difficult and time-consuming (as it often requires

negotiations between multiple competitors), FDA has waived the shared REMS requirement only once, in the case of buprenorphine. *See generally* Food and Drug Administration, *FDA/CDER to Reckitt Benckiser Pharmaceuticals, Inc.—Petition Denial (Docket No. FDA-2012-P-1028)*, REGULATIONS.GOV (Feb. 22, 2013). Indeed, there are currently six shared REMS programs involving over 40 participating sponsors, and the shared REMS program for extended-release and long-acting opioid analgesics has achieved coordination among 24 sponsors. Food and Drug Administration, *Approved Risk Evaluation and Mitigation Strategies (REMS)*, FDA.gov (June 11, 2014), *available at* http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm111350.htm.

II. Factual Background

A. Prometheus' LOTRONEX®

18. Prometheus is a biotechnology company with a primary focus in novel pharmaceutical and diagnostic products. Since 2008, Prometheus has invested over $113 million developing and commercializing LOTRONEX®, and sales of LOTRONEX ® accounted for approximately 25% of Prometheus' revenues in 2014. Revenues from LOTRONEX ® are used to fund Prometheus' investment in promising new pharmaceutical and diagnostic products. Alonso Declaration ¶ 6.

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

20. On February 9, 2000, FDA approved LOTRONEX® to treat IBS in women whose predominant bowel symptom is diarrhea. As the first drug approved to treat IBS-D, LOTRONEX® was met with strong patient demand. Within 10 months, 325,000 patients were taking LOTRONEX®.

21. 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. However, it was not off the market for long. Sufferers of severe IBS-D, their doctors, and their supporters—even a congressman—deluged FDA with letters, explaining that alosetron was the only treatment that worked for them, and demanding that the agency work with the drug's manufacturer to return alosetron to the market.

22. On June 7, 2002, FDA approved a supplement to the NDA for LOTRONEX® 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 prescribers into a prescribing program, an education program for prescribers, pharmacists and patients about the risks and benefits of LOTRONEX®, the collection and reporting of serious adverse events associated with

the use of LOTRONEX®, and the ongoing evaluation of the effectiveness of the risk management program.

23. Prometheus acquired LOTRONEX® on October 31, 2007 from the drug's original sponsor, and promptly submitted a REMS for the drug, as required for drugs originally approved with required restrictions and deemed to have an approved REMS with the enactment of the Food and Drug Amendments Act of 2007 (FDAAA) which established the agency's REMS authority. On September 2, 2010, FDA approved the LOTRONEX® REMS. Ex. 1. 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. *See* Ex. 2 (excerpt); *see also* Prometheus REMS at http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM227960.pdf. All components of the REMS work together and are required by FDA as necessary for the safe use of LOTRONEX®.

B. Roxane's ANDA and Prometheus' Attempts to Negotiate a Single Shared REMS

24. On October 14, 2009, Roxane submitted an ANDA seeking permission to market a purported generic version of LOTRONEX®. Upon being contacted by Roxane to begin discussions regarding a shared REMS for alosetron, Prometheus began good faith negotiations with Roxane to develop a single, shared REMS as required by 21 U.S.C. § 355-1(i)(1)(B). Prometheus spent substantial time and effort in attempting to develop a single, shared REMS with Roxane.

Unfortunately, Roxane ceased participating in the negotiations in June 2014 with no explanation for the reason for ceasing negotiations.

25. On May 10, 2013, Prometheus submitted a Citizen Petition to FDA. Ex. 3. Among other things, Prometheus requested that it be given notice and the opportunity to participate in any process used by FDA to determine whether to grant a waiver from the requirement for a single, shared REMS for LOTRONEX. *Id.*

26. On October 7, 2013, FDA responded to Prometheus' Citizen Petition. Ex. 4. While FDA denied Prometheus' request to be given notice of an application for a waiver of the single, shared REMS requirement, FDA noted that Prometheus was free to submit its views on whether the burdens of creating a single, shared system outweigh the benefits. *Id.* at 7. Despite Prometheus' requests, FDA failed to provide any substantive guidance on the process for competitors to come together to create a single, shared REMS and failed to provide any guidance on the standard for granting a waiver.

27. On June 30, 2014, Prometheus filed a letter with FDA opposing Roxane's request for a waiver from the statutory mandate that generic drugs share a single REMS with their RLDs. Ex. 5.

28. For the next ten months up until the FDA approved Roxane's ANDA, Prometheus continued to express to Roxane and FDA its belief that a shared REMS was in the interest of the healthcare system and the patients and its willingness to develop a shared REMS and worked diligently to try to elicit FDA's help in inducing Roxane to negotiate a single, shared REMS as required by the statute, sending numerous emails to the agency imploring for assistance in getting Roxane to the table. Neither FDA nor Roxane responded substantively to those efforts. Among other things, Prometheus provided Roxane a draft proposal for a single, shared REMS and Roxane never

responded to the proposal. In the absence of further guidance from FDA, Prometheus followed the only guidance provided by FDA on shared REMS (which was contained in FDA's response to Prometheus' Citizen Petition), which described a process in which the parties would continue to negotiate a shared REMS. FDA never engaged with Prometheus to explain the burden on Roxane in creating a single, shared REMS or how that burden was significant enough to outweigh the impact on patients and the health care system in navigating two separate REMS.

29. On January 30, 2015, Prometheus wrote to FDA again, to reiterate its commitment to developing a single, shared REMS and its belief that a single, shared REMS was in the interests of the patients, the healthcare system and the drug sponsors, and again requested that FDA assist with efforts to induce Roxane to participate in discussions regarding a shared REMS. Ex. 6. FDA did not respond.

30. On May 4, 2015, FDA approved Roxane's ANDA. Ex. 7. Although FDA purported to waive the statutory requirement mandating a single, shared REMS, FDA justified doing so by attaching two unauthorized qualifications to the waiver: (1) that the waiver-granted REMS system shall be open to all current and future sponsors of ANDAs or NDAs for alosetron hydrochloride products and (2) the waiver was limited to a term of three years. *Id.* at 2-3. FDA failed to explain how the Roxane REMS would be open to current and future sponsors of alosetron hydrochloride, or how the expiration of the waiver would work – whether Roxane's approval would be withdrawn, or whether Roxane would instead be subject to Prometheus' REMS. FDA also failed to explain how the burdens of creating a single, shared system outweighed the benefit of a single, shared REMS as required by 21 U.S.C. § 355-1(i)(1)(B)(i).

31. FDA posted Roxane's REMS on its website on May 11, 2015. *See* Ex. 8 (excerpt); *see also* Roxane REMS at http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM446436.pdf. Contrary to the requirements of 21 U.S.C. § 355-1(i)(1)(B)(i), the ETASU that are contained in Roxane's REMS is not "comparable" to the ETASU in the REMS for LOTRONEX®, the RLD upon which Roxane's drug was approved, most importantly because Roxane's REMS appears to permit the dispensing of Roxane's product pursuant to prescriptions by healthcare providers that are not enrolled in the Roxane REMS. *Id*. at 5, n. 1.

32. The denial of Prometheus' Citizen Petition and approval of Roxane's ANDA means that Prometheus has exhausted its administrative remedies.

III. FDA's Conduct is Unlawful, Arbitrary and Capricious

33. FDA's decision to approve Roxane's ANDA and to grant a waiver of the single, shared REMS violates the FDCA, including but not limited to 21 U.S.C. §§ 355(b), 355(j), 355-1(a), 355-1(i), and 502(p).

34. Because the FDCA does not authorize FDA to attach conditions or qualifications to a waiver of the share REMS, FDA acted arbitrary, capriciously, and contrary to law when it attached conditions to Roxane's waiver of the single, shared REMS. 21 U.S.C. § 355-1(i)(1)(B).

35. FDA also acted arbitrary, capriciously, and contrary to law in granting the waiver because the burden of creating a single, shared system does not outweigh the benefit of such a system. *See* 21 U.S.C. § 355-1(i)(1)(B)(i). Waiving the requirement for a single, shared REMS significantly increases, rather than eases, the burdens on the health care delivery system. For example, separate

REMS for LOTRONEX® and Roxane's product require prescribers to comply with distinct sets of requirements, which would amplify the time required for paperwork, verification, documentation, patient education, and other REMS obligations. Separate REMS would also complicate the requirements for pharmacists, who would need to follow different procedures based on which sticker is affixed to each alosetron prescription. Pharmacists also would have to navigate the challenge of complying with generic substitution requirements under state laws and payors' policies, on the one hand, and complying with the provisions of two distinct REMS established under federal law, on the other hand. The footnote in Roxane's REMS purporting to allow pharmacists to substitute generic alosetron when filling a prescription with a LOTRONEX® sticker does not obviate the problem and raises myriad issues of its own. *See* Ex. 8 at at 5, n. 1. For patients, two separate REMS would almost certainly increase the likelihood of prescribing and dispensing errors and could compromise the clarity and quality of the communications that patients need to receive from prescribers and pharmacists to assure the safe use of alosetron hydrocholoride. Prescribers may see their patients receiving a drug covered by a REMS that does not correspond to the REMS into which the prescriber is enrolled and does not correspond to the patient materials that were provided to the patient. The required surveys of pharmacists, prescribers and patients to monitor and evaluate compliance with the requirements of the particular REMS may be sent to and completed by parties that did not prescribe, dispense or use the drug covered by the REMS being evaluated. The heightened burdens and risks associated with two separate REMS could have a negative impact on the public health by discouraging treatment of patients with severe diarrhea-predominant IBS, decreasing prescriber compliance with any alosetron REMS, and/or promoting greater use of alternate medications that are not subject to a REMS, but that

are less effective or less therapeutically appropriate for this condition. Moreover, the administrative costs to prescribers and pharmacists in complying with multiple separate REMS and the resulting confusion may diminish patient access to alosetron and lead providers to prescribe other treatments which are less clinically therapeutic or appropriate for severe IBS-D. There simply is no basis upon which FDA could have found that these burdens are outweighed by any burden on the generic or the innovator. This is especially true because the innovator was repeatedly expressing its belief that a shared REMS could be worked out and would be to the benefit to all parties and Roxane walked away from an active negotiation with no explanation of what, in its view, a shared REMS should even look like. FDA simply had no basis for determining that the burden on Roxane of a shared REMS outweighed the benefits thereof.

36. FDA also acted arbitrary, capriciously, and contrary to law in granting the waiver because Roxane's REMS does not include Elements to Assure Safe Use that are comparable to the Elements to Assure Safe Use in Prometheus' REMS as required by 21 U.S.C. § 355-1(i)(1)(B). Roxane's REMS permits the dispensing of Roxane's product pursuant to prescriptions by healthcare providers that are not enrolled in the Roxane REMS. Ex. 8 at 5, n. 1. The LOTRONEX® REMS includes a safe use condition that has been key to the safe use of LOTRONEX® since it was reintroduced to the market in 2002 and reaffirmed by FDA as necessary for the safe use of LOTRONEX® with the approval of the LOTRONEX® REMS in 2008; that LOTRONEX® only be dispensed by a certified pharmacy pursuant to a prescription issued by a prescriber enrolled in the LOTRONEX® REMS. To the contrary, through a short footnote, Roxane's REMS appears to permit the dispensing of its product pursuant to a prescription by a provider not enrolled in Roxane's REMS,

at least in certain states. *Id*. In addition, like the LOTRONEX® REMS, the Roxane REMS includes an Implementation System requiring Roxane to monitor compliance with the Roxane REMS, including ensuring its product is prescribed by prescribers enrolled in its REMS and that patients are only treated with its product following documentation of safe-use condition. However, the Roxane REMS appear to permit the dispensing of its product pursuant to prescriptions by prescribers not enrolled in Roxane's REMS and to patients for whom Roxane has provided no patient acknowledgement forms. The gutting of the safe use condition in Roxane's REMS prohibits Roxane from carrying out the requirements in the Implementation System to monitor, evaluate and work to improve the REMS ETASU and will certainly render Roxane's REMS as fundamentally different, and less effective, than the Prometheus REMS. Finally, at the most basic and most important level, the Roxane REMS is not comparable in that it will not ensure the same level of safe use of the Roxane product as the LOTRONEX® REMS.

37. FDA's approval of Roxane's ANDA and conditional waiver of the statutory requirement for a single, shared REMS reflects a failure to engage in reasoned decision making.

38. FDA's approval of Roxane's ANDA and conditional waiver of the statutory requirement for a single, shared REMS was not in accordance with federal law and therefore violates 5 U.S.C. § 706(2)(A).

39. FDA's approval of Roxane's ANDA and conditional waiver of the statutory requirement for a single, shared REMS also constitutes agency action in excess of statutory jurisdiction, authority, or limitations, or short of statutory right, in violation of 5 U.S.C. § 706(2)(C).

IV. FDA's Actions Will Cause Immediate and Irreparable Harm to Patients and Prometheus

40. FDA's unlawful conduct poses a very real imminent risk to the public. The separate REMS will increase burdens on prescribers and pharmacists in complying with two different systems and procedures. For patients, two separate REMS would almost certainly increase the likelihood of prescribing and dispensing errors and could compromise the clarity and quality of the communications that patients need to receive from prescribers and pharmacists to assure the safe use of alosetron hydrocholoride. Ultimately, the heightened burdens and risks associated with two separate REMS could have a negative impact on the public health by discouraging treatment of patients with severe diarrhea-predominant IBS, decreasing prescriber compliance with any alosetron REMS, and/or promoting greater use of alternate medications that are not subject to a REMS, but that are less effective or less therapeutically appropriate for this condition. The frustration, ill will, and increased costs experienced by prescribers, pharmacists, and patients in complying with two separate REMS will negatively affect Prometheus.

41. FDA's unlawful conduct also threatens Prometheus with grave irreparable harm. FDA's approval of Roxane's ANDA opens the door for Roxane to flood the market with its purported "generic" version of LOTRONEX® immediately. It is well known in the pharmaceutical industry that generic drugs quickly take over the market soon after their launch. The impact on Prometheus would be commercially devastating. Revenues from LOTRONEX® currently comprise over 25% of Prometheus' revenues, permitting the company to invest in promising new pharmaceutical and diagnostic products. Alonso Declaration ¶ 6. New generic entrants into the market have an immediate

and precipitous effect upon both market share and the pricing of the brand name drugs upon which they are based. For instance, generic drugs usually capture approximately 50% of the market in the first month and about 90% or more of the market within the next five months. *Id.* ¶ 5. There is no mechanism by which Prometheus can be made whole for the injury that would result from the unlawful entry into the marketplace of Roxane's purported generic drug. And because the foregoing losses never can be recovered from FDA, Prometheus will be irreparably harmed unless FDA's conduct is enjoined promptly.

42. Conversely, neither FDA nor Roxane will suffer any significant hardship if approval of Roxane's ANDA is enjoined. An injunction would simply maintain the status quo pending full consideration on the merits. In any event, neither FDA nor Roxane has an interest in violating the FDCA.

43. The intent of Congress will be served by an Order directing FDA to rescind its approval of Roxane's ANDA. In addition, such an Order will serve the public interest by prohibiting unnecessary burdens on the healthcare system and requiring FDA to comply with its obligations.

44. FDA's denial of Prometheus's Citizen Petition and approval of Roxane's ANDA constitutes final agency action for which Prometheus has no other adequate remedy within the meaning of 5 U.S.C. § 704.

Count I
(Administrative Procedure Act: Violation of the FDCA and Applicable Regulations)

45. Prometheus re-alleges, reasserts, and incorporates by reference herein each of the allegations contained in paragraphs 1 through 44 of the Verified Complaint as though set forth fully herein.

46. FDA's denial of Prometheus' Citizen Petition, decision to approve Roxane's ANDA, and other agency action and inaction described herein was unlawful and in violation of the FDCA and the agency's own policies and procedures.

47. FDA's denial of Prometheus' Citizen Petition, decision to approve Roxane's ANDA, and other agency action and inaction described herein constitutes final agency action for which Prometheus has no other adequate remedy within the meaning of 5 U.S.C. § 704.

48. FDA's denial of Prometheus' Citizen Petition, decision to approve Roxane's ANDA, and other agency action and inaction described herein was not in accordance with federal law and therefore violates 5 U.S.C. § 706(2)(A).

49. FDA's denial of Prometheus' Citizen Petition, decision to approve Roxane's ANDA, and other agency action and inaction described herein constitutes agency action in excess of statutory jurisdiction, authority, or limitations, or short of statutory right, in violation of 5 U.S.C. § 706(2)(C).

50. Both Prometheus and the health care system will be irreparably harmed unless FDA is enjoined from approving – or, alternatively, required to withdraw its approval of – Roxane's ANDA.

51. There is no mechanism by which Prometheus can be made whole for the injury that would result from the entry into the marketplace of an unlawful alosetron hydrochloride product. Prometheus is without an adequate remedy at law because of the unique nature of the harm.

52. The intent of Congress will be served by an Order directing FDA to withdraw its approval of Roxane's ANDA. In addition, the public interest will be served by such an Order.

Count II
(Administrative Procedure Act: FDA's Conduct Was Arbitrary, Capricious, an Abuse of Discretion and Contrary to Law)

53. Prometheus re-alleges, reasserts, and incorporates by reference herein each of the allegations contained in paragraphs 1 through 52 of the Verified Complaint, as though set forth fully herein.

54. The APA prohibits FDA from implementing the FDCA in a manner that is arbitrary, capricious, or an abuse of discretion. 5 U.S.C. § 706(2)(A).

55. FDA's denial of Prometheus' Citizen Petition and decision to approve Roxane's ANDA was not based on reasoned decision or rational basis, and therefore was arbitrary, capricious, an abuse of discretion and otherwise not in accordance with law in violation of 5 U.S.C. § 706(2)(A).

56. FDA's denial of Prometheus' Citizen Petition and decision to approve Roxane's ANDA was premised on agency determinations that represented abrupt departures from long-standing agency practice and treated similarly-situated entities differently. FDA's conduct was arbitrary, capricious, an abuse of discretion and otherwise not in accordance with law in violation of 5 U.S.C. § 706(2)(A).

57. FDA's denial of Prometheus' Citizen Petition and decision to approve Roxane's ANDA violates FDA's own regulations and governing statute, in violation of the APA.

58. FDA's denial of Prometheus' Citizen Petition and decision to approve Roxane's ANDA constitutes final agency action for which Prometheus has no other adequate remedy within the meaning of 5 U.S.C. § 704.

59. Both Prometheus and the patient population will be irreparably harmed unless FDA is required to withdraw its approval of Roxane's ANDA.

60. There is no mechanism by which Prometheus can be made whole for the injury that would result from the entry into the marketplace of Roxane's product. Prometheus is without an adequate remedy at law because of the unique nature of the harm.

61. The intent of Congress will be served by an Order directing FDA to withdraw its approval of Roxane's ANDA. In addition, the public interest will be served by such an Order.

PRAYER FOR RELIEF

WHEREFORE, plaintiff respectfully prays for the following relief:

A. A declaration pursuant to 28 U.S.C. § 2201 that FDA's decision to approve Roxane's ANDA was arbitrary, capricious, and contrary to law under the APA and the FDCA;

B. A declaration pursuant to 28 U.S.C. § 2201 that FDA's denial of Prometheus' Citizen Petition was arbitrary, capricious and contrary to law under the APA and the FDCA;

C. Temporary, preliminary and permanent injunctive relief enjoining, requiring FDA to rescind or—at the very least—stay its approval of Roxane's ANDA;

D. An order awarding plaintiff's costs, expenses and attorneys' fees pursuant to 28 U.S.C. § 2412; and

E. Such other and further relief as the Court deems just and proper.

Respectfully submitted,

Susan Cook /EAJ

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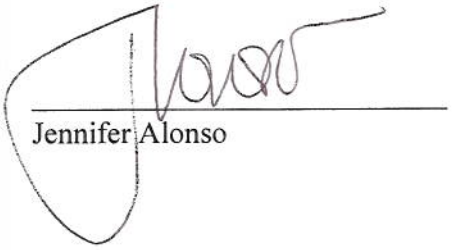
Attorneys for Plaintiff Prometheus Laboratories Inc.

Dated: May 18, 2015

VERIFICATION

I, the undersigned, having read the allegations of the foregoing Verified Complaint, hereby declare under penalty of perjury and pursuant to 28 U.S.C. § 1746 that the factual allegations asserted in the Verified Complaint are true and correct based on my personal knowledge and on information derived from the business records of Prometheus Laboratories Inc. I further declare that matters asserted upon information and belief are believed to be true and correct.

Executed this 18th day of May, 2015.



Jennifer Alonso