IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

PROMETHEUS LABORATORIES INC., Plaintiff, v. SYLVIA MATHEWS BURWELL, in her official capacity as SECRETARY, UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES, and STEPHEN OSTROFF, M.D., in his official capacity as ACTING COMMISSIONER OF FOOD AND DRUGS, FOOD AND DRUG ADMINISTRATION, Defendants.	Civil Action No. _____

MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF PLAINTIFF'S MOTION FOR TEMPORARY RESTRAINING ORDER AND/OR PRELIMINARY INJUNCTION

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TABLE OF CONTENTS

Page(s)

TABLE OF AUTHORITIES

Page(s)

CASES

STATUTES

INTRODUCTION

Plaintiff Prometheus Laboratories Inc. ("Prometheus") seeks a TRO or preliminary injunction to temporarily suspend FDA's recent approval of 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), for permission to market a purported generic version of Prometheus' LOTRONEX® (alosetron hydrochloride tablets). In approving Roxane's purported generic drug, FDA unlawfully waived distribution and marketing restrictions applicable to LOTRONEX®. FDA's approval was therefore arbitrary, capricious, and unlawful under the Administrative Procedure Act ("APA").

Prometheus' LOTRONEX® is an FDA-approved drug used to treat severe Irritable Bowel Syndrome in women whose predominant bowel symptom is diarrhea ("IBS-D"). As the first drug approved to treat IBS-D, LOTRONEX® provides important benefits to patients. It also presents some risks, however. As a result, LOTRONEX® may only be marketed under a Risk Evaluation and Mitigation Strategy ("REMS"), which is a set of requirements on the distribution and marketing of a drug product imposed by FDA to ensure that the benefits of the drug outweigh its risks. The FDCA expressly mandates that FDA must require generic drugs to use a single, shared REMS with the reference drug, unless the generic applicant qualifies for a statutory waiver. The statute contemplates only two options: either a generic drug qualifies for a waiver of the reference drug's REMS or it does not. 21 U.S.C. § 355-1(i)(1)(B). In approving Roxane's generic version of LOTRONEX®, however, FDA expressly attached two conditions to its grant of a waiver of the statutorily required single, shared REMS. 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 APA.

In addition, FDA's grant of a waiver also was unlawful, arbitrary and capricious under the APA because it failed to comply with the FDCA's express statutory requirements for a waiver. First, the statute requires that the burden to the ANDA applicant involved in developing a single shared REMS must outweigh the benefits to the healthcare system associated with a shared REMS. 21 U.S.C. § 355-1(i)(1)(B). Here, whatever burden might exist for Roxane in developing a single, shared REMS for alosetron is clearly outweighed by the benefits to the healthcare system and patients of using a single shared REMS. And second, the statute requires that in order to qualify for a waiver, the generic product's REMS must include "comparable aspects" of the "elements to assure safe use" contained in the LOTRONEX® REMS. 21 U.S.C. § 355-1(i)(1)(B). The Roxane REMS fails to meet this requirement here.

The four factors governing injunctive relief strongly favor issuance of an injunction in this case. Prometheus' likelihood of success is strong. FDA does not have statutory authority to attach conditions to a waiver of a single shared REMS. Yet here it did just that, twice. Additionally, FDA improperly applied the statutory guidelines in determining to issue a waiver, for two separate reasons. First, as noted above, the burden of creating a single, shared system does not outweigh the benefit of a single system as required by 21 U.S.C. § 355-1(i)(1)(B)(i). And second, Roxane's REMS does not include "elements to assure safe use" comparable to those set forth in Prometheus' REMS as required by 21 U.S.C. § 355-1(i)(1)(B). Granting an injunction will promote the public interest by protecting patients and the health care system from the burdens and risks associated with complying with two separate REMS systems. In the absence of immediate injunctive relief, Prometheus will suffer irreparable injury. Absent immediate injunctive relief, Roxane's drug will immediately overtake LOTRONEX®'s market share, drive down prices, and have a devastating effect on Prometheus' ability to invest in R&D

for pipeline products and otherwise support commercial operations. The requested injunctive relief will cause no undue hardship to FDA or to Roxane, since it simply preserves the status quo pending briefing on the merits.

STATEMENT OF FACTS

1. Statutory Background

A. The Drug Approval Process

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 New Drug Application ("NDA"). 21 U.S.C. § 355(b)(1). 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).

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 conclusion 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.

B. Risk Evaluation And Mitigation Strategies (REMS)

FDA has authority to require a REMS at the time of a new drug approval or after approval based on new safety data 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.

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 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 and the innovator product must use a single, shared REMS to mitigate the risks of both the innovator and the generic product. 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.

FDA may waive the statutory requirement for a single, shared REMS and allow the generic product to come to market with a REMS that includes "a different, comparable aspect of the elements to assure safe use" 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) (emphasis added). The structure and language of the statute make clear that a single, shared REMS is the norm, and approval of a separate REMS with comparable ETASU 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 a generic drug and the RLD share a single shared REMS. *Id.*

2. Factual Background

A. FDA Approval of LOTRONEX®

On February 9, 2000, FDA approved LOTRONEX® to treat severe IBS in women whose predominant bowel symptom is diarrhea, known as IBS-D. Verified Complaint ¶ 20. As the

first drug approved to treat IBS-D, LOTRONEX® was met with strong patient demand. 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). *Id.* ¶ 21. The agency held a public advisory committee meeting on June 27, 2000 to discuss these adverse events and risk-management options. *Id.* On November 28, 2000, LOTRONEX® was voluntarily withdrawn from the market. *Id.* There was an immediate public outcry from affected parties. 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. *Id.*

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. Verified Complaint ¶ 22. 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. *Id.*

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"). Verified Complaint ¶ 23. On September

2, 2010, FDA approved the LOTRONEX® REMS. Verified Complaint, 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. *Id.* All components of the REMS work together and are necessary for the safe use of LOTRONEX®.

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

On October 14, 2009, Roxane submitted an ANDA seeking permission to market a purported generic version of LOTRONEX®. Verified Complaint ¶ 24. 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). *Id.* Prometheus spent substantial time and effort in attempting to develop a single, shared REMS with Roxane. *Id.* Unfortunately, Roxane ceased participating in the negotiations in June 2014 with no explanation for the reason for ceasing negotiations. *Id.*

On May 10, 2013, Prometheus submitted a Citizen Petition to FDA. Verified Complaint, 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.*

On October 7, 2013, FDA responded to Prometheus' Citizen Petition. Verified Complaint, 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.

On June 30, 2014, after Roxane ceased participating in Prometheus' efforts to negotiate a shared REMS, 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. Verified Complaint, Ex. 5. For the next ten months, up and until 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 patients, as well as its willingness to develop a single, shared REMS. Verified Complaint ¶ 28. Prometheus even sent a draft of a single shared REMS to Roxane. *Id.* But Roxane never commented on it. *Id.* Prometheus also 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. *Id.* Neither FDA nor Roxane responded to those requests. *Id.*

On January 30, 2015, Prometheus again wrote to FDA to reiterate its commitment to developing a single, shared REMS and its continued belief that a single, shared REMS was in the interests of patients, the healthcare system and the drug sponsors. Prometheus again requested that FDA assist with efforts to induce Roxane to participate in discussions regarding a single, shared REMS. Verified Complaint, Ex. 6. FDA failed to respond to that letter.

On May 4, 2015, FDA approved Roxane's ANDA, with its own separate REMS. Verified Complaint, 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) Roxane's REMS must be open to all current and future sponsors of ANDAs or NDAs for alosetron hydrochloride products; and (2) the waiver is 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 – for example, whether Roxane's approval would be withdrawn, or if Roxane instead would be subject to Prometheus' REMS. *Id.* at 3. 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). *Id.*

On May 11, 2015, FDA posted Roxane's REMS on its website. Verified Complaint ¶ 31. Contrary to the requirements of 21 U.S.C. § 355-1(i)(1)(B)(i), the Elements to Assure Safe Use in Roxane's REMS are not "comparable" to the Elements To Assure Safe Use in the REMS for LOTRONEX®. Because Roxane's REMS permits the dispensing of Roxane's product pursuant to prescriptions by healthcare providers that are not enrolled in the Roxane REMS, the Roxane REMS will not ensure the same level of safe use of Roxane's product as the LOTRONEX® REMS. Verified Complaint ¶ 31.

C. The Need for Immediate Judicial Intervention

Upon information and belief, Roxane is poised to launch its drug at any moment using its separate REMS. Verified Complaint ¶ 41. FDA's actions pose a substantial and imminent harm to patients, prescribers, and pharmacists due to the increased burdens and heightened risk of errors in navigating two separate REMS. *Id.* ¶ 40. FDA's actions also will irreparably harm Prometheus. Introduction of a low-cost purported generic will have an immediate and dire effect on Prometheus' sales of LOTRONEX®, which currently comprise 25% of the company's total revenues. Verified Complaint ¶ 41; Alonso Declaration ¶ 6. Such losses will have a devastating effect on Prometheus' support for existing products and investment in pipeline products. *Id.* 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 drug. Judicial intervention therefore is necessary to prevent devastating harm.

ARGUMENT

The standards governing issuance of a TRO or preliminary injunction are well known. *See Morgan Stanley DW Inc. v. Rothe*, 150 F. Supp. 2d 67, 72 (D.D.C. 2001). The movant must show: "(1) a substantial likelihood of success on the merits, (2) that it would suffer irreparable injury if the injunction is not granted, (3) that an injunction would not substantially injure other interested parties, and (4) that the public interest would be furthered by the injunction." *Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060, 1066 (D.C. Cir. 1998) (citation omitted). All four of these factors mandate entry of injunctive relief here.

I. PLAINTIFF HAS A STRONG LIKELIHOOD OF SUCCESS ON THE MERITS.

The APA provides that a court "shall . . . hold unlawful and set aside agency action, findings, and conclusions found to be . . . arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). It is well settled that an agency acts unlawfully when it violates its governing statute. *See, e.g., Bennett v. Donovan*, 4 F. Supp. 3d 5, 13 (D.D.C. 2013).

And even when an agency is granted discretion by Congress, it is not enough for the agency simply to cite to a set of facts and draw an ultimate conclusion from those facts without connecting the dots in between; rather, it must "examine the relevant data and articulate a satisfactory explanation for its action including **a rational connection between the facts found and the choice made**." *Tripoli Rocketry Ass'n, Inc. v. Bureau of Alcohol, Tobacco, Firearms, and Explosives*, 437 F.3d 75, 81 (D.C. Cir. 2006) (emphasis added). As the D.C. Circuit has noted, "where an agency has articulated no reasoned basis for its decision – where its action is

founded on unsupported assertions or unstated inferences – we will not 'abdicate the judicial duty carefully to 'review the record to ascertain that the agency has made a reasoned decision based on reasonable extrapolations from some reliable evidence.'" *Id.* at 83. Thus, in order to survive scrutiny under the APA, "'an agency must cogently explain why it has exercised its discretion in a given manner,' and that explanation must be 'sufficient to enable us to conclude that the [agency's action] was the product of reasoned decisionmaking.'" *A.L. Pharma, Inc. v. Shalala*, 62 F.3d 1484, 1491 (D.C. Cir. 1995) (internal citation omitted). *See also, e.g., Homer v. Roche*, 226 F. Supp. 2d 222, 226-27 (D.D.C. 2002) (where agency's reasoning is "entirely opaque," agency has not provided the requisite "'rational connection between the facts found and the choice made'") (quotation omitted); *Natural Res. Def. Council, Inc. v. Daley*, 209 F.3d 747, 755-56 (D.C. Cir. 2000) ("The Service cannot rely on reminders that its scientific determinations are entitled to deference in the absence of reasoned analysis to cogently explain why its recommended measures satisfied [statutory] requirements.") (quotations omitted).

Judicial review of agency action requires a "searching and careful" inquiry into the basis for the agency's decision. *Zotos Int'l, Inc. v. Young*, 830 F.2d 350, 352 (D.C. Cir. 1987). The reviewing court may give deference to an agency's scientific judgments to the extent they are consistent and reasonable, but the court does "not hear cases merely to rubber stamp agency actions. To play that role would be tantamount to abdicating the judiciary's responsibility under the [APA]." *Natural Res. Def. Council, Inc.*, 209 F.3d at 755 (quotation omitted). In other words, while courts defer to an agency's substantiated scientific judgments, the emphasis is very much on "substantiated." Mere assertions of agency expertise will not do; the agency must show its work.

FDA fails all of these tests.

A. FDA Lacks Statutory Authority to Attach Conditions to A REMS Waiver.

FDA lacks statutory authority to attach conditions in order to justify waiver of a single, shared REMS. The FDCA states, in relevant part:

> The Secretary may waive the requirement under the preceding sentence for a drug that is the subject of an abbreviated new drug application, and permit the applicant to use a different, comparable aspect of the elements to assure safe use, if the Secretary determines that—
>
> > (i) the burden of creating a single, shared system outweighs the benefit of a single, system, taking into consideration the impact on health care providers, patients, the applicant for the abbreviated new drug application, and the holder of the reference drug product….

21 U.S.C. § 355-1(i)(1)(B). The plain language of the statute does not grant FDA the authority to attach conditions to a waiver. *Id.*[1] Either the standard is met for a waiver or it is not; the statute permits FDA no authority to attach conditions to grant a modified waiver in order to overcome an applicant's failure to meet the standard. *Id.*

Yet when FDA approved Roxane's waiver of a single, shared REMS on May 4, 2015, the agency took the unprecedented action of utilizing "conditions" in order to justify a waiver. Specifically, FDA stated that Roxane would be granted a waiver "subject to two conditions": (1) the new Roxane REMS system "shall be open to all current and future sponsors of ANDAs or NDAs for alosetron hydrochloride products"; and (2) the waiver is limited to a term of three years. Verified Complaint, Ex. 7 at 2-3. In its approval, FDA failed to explain how it had the statutory authority to attach conditions, why the two conditions were warranted, or whether

[1] Nor is this an issue upon which FDA should be given deference. When an agency acts or interprets a statute in a manner that is "contrary to clear congressional intent," courts owe the agency's interpretation no deference. *Chevron USA, Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837, 843 & n.9 (1984); *see also Depomed, Inc. v. HHS*, -- F. Supp. 2d --, 2014 WL 4457225, *9 (D.D.C. Sept. 5. 2014).

Roxane's waiver application would have met the standard without the two conditions attached. Verified Complaint, Ex. 7.

Nor is it even clear how the conditions would operate. One of the conditions is that Roxane's REMS must be "open to all current and future sponsors of … NDAs for alosetron hydrochloride." Verified Complaint, Ex. 7 at 2-3. But Prometheus has been trying to negotiate a shared REMS with Roxane, and Roxane simply stopped responding to Prometheus' communications. Verified Complaint ¶ 28. FDA is well aware of this fact, because Prometheus has sought FDA's assistance in inducing Roxane to come to the negotiation table for months. *Id.* It defies all logic, then, for FDA to approve an ANDA and grant a waiver from the requirement of a single, shared REMS on a condition that Roxane make its REMS open to Prometheus.

Because the FDCA does not authorize the agency to impose non-statutory conditions in order to justify a waiver, FDA's approval of Roxane's ANDA was unlawful and contrary to statute.

B. FDA's Decision to Grant the Waiver Violates the FDCA.

Separately, FDA's decision to waive the shared REMs requirement also violates the FDCA because none of the statutory requirements for a waiver are met here. First, Roxane's waiver does not meet the statutory requirement that the burden of creating a single, shared system not outweigh the benefits to the health care system and patients. 21 U.S.C. § 355-1(i)(1)(B)(i). And second, the ETASU set forth in Roxane's REMS are not "comparable" to those in Prometheus's REMS, as required by the FDCA. 21 U.S.C. § 355-1(i)(1)(B).

1. The Burden of Creating a Single Shared System Does Not Outweigh the Benefit.

FDA may waive the requirement that a reference drug and a generic utilize a single, shared REMS only if "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." 21 U.S.C. § 355-1(i)(1)(B)(i). FDA has not made any showing that this standard is met. Indeed, in its approval, FDA failed to even attempt to explain how the burdens of creating a single, shared system outweighed the benefit of a single shared REMS pursuant to 21 U.S.C. § 355-1(i)(1)(B)(i). FDA likewise failed to respond to any of the significant concerns expressed in Prometheus' June 30, 2014 letter (and reiterated in its January 30, 2015 letter) about the impact on patient safety, public health, and the health care system of two separate REMS for alosetron hydrochloride tablets. FDA thus violated its duties under 21 U.S.C. § 355-1(i)(1)(B)(i).

Under the FDCA, FDA must weigh any burdens associated with negotiating the single, shared REMS against "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." 21 U.S.C. § 355-1(i)(1)(B)(i). It cannot seriously be disputed that a single, shared REMS would provide numerous benefits. Separate REMS would 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. Verified Complaint ¶ 35. Separate REMS also would complicate the requirements for pharmacists, who would need to follow different procedures based on which sticker is affixed to each alosetron prescription. *Id.* 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. *Id.*[2] And for patients, two separate REMS would 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. *Id.* Prescribers may find their patients receiving 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. *Id.* The required surveys of pharmacists, prescribers, 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. *Id.*

Moreover, the administrative costs to providers and pharmacists in complying with two 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 IBS-D. *Id.* FDA's approval of Roxane's waiver addresses none of these very real costs and burdens on the health care system associated with two separate REMS.

In contrast, there simply is no undue burden in creating a single shared REMS. Prometheus has bent over backward to cooperate with Roxane throughout this process, believing and repeatedly stating to Roxane and FDA that a single shared REMS is in the best interest of patients and the health care delivery system. Verified Complaint ¶ 28. To that end, Prometheus worked diligently with Roxane attempting to agree upon a single, shared REMS – right up until Roxane unilaterally ceased negotiating. Verified Complaint ¶¶ 24, 28. Prometheus even

[2] Although much of the language in the REMS is similar, a critical footnote in Roxane's REMS purports to allow pharmacists to substitute generic alosetron when filling a prescription with a LOTRONEX® sticker. Verified Complaint, Ex. 8, at 5 n. 1. This creates an enormous administrative burden, as set forth in argument section II, infra.

provided Roxane a draft proposal for a single, shared REMS, and Roxane never responded to the proposal. Verified Complaint ¶ 28. Thus, FDA abused its discretion in finding the burdens of a single, shared REMS outweighed the benefits when a proposed single, shared REMS was on the table with no response from Roxane.

Even after negotiations with Roxane ground to a halt, Prometheus repeatedly sought FDA's assistance in restarting the negotiations for a single, shared REMS, with virtually no substantive contact from FDA. *Id.* Despite Prometheus' requests, FDA failed to provide any 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. Verified Complaint, Ex. 4. 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 or what Prometheus could do to mitigate that burden. Verified Complaint ¶ 28. FDA therefore abused its discretion and acted contrary to law.

2. The ETASUs in Roxane's REMS are not comparable to those in Prometheus' REMS.

By statute, FDA may only grant a waiver if the "different" "aspect[s] of the elements to assure safe use" are "comparable" to the ETASUs for the reference drug. 21 U.S.C. § 355-1(i)(1)(B). FDA acted arbitrarily and capriciously and contrary to law in approving ETASUs for Roxane that are not comparable to those required under Prometheus' REMS. While the ETASUs for both REMS are, on their surface, fairly similar in nature (both require prescriber education and enrollment, both require the dispensation of information to patients, and both prohibit pharmacists from dispensing the drug unless the prescription contains a sticker

demonstrating the prescriber's compliance with the REMS program), the Roxane REMS contains a key footnote that renders its ETASU not comparable to Prometheus's REMS. That footnote says: "In the alternative, a prescription for alosetron may be dispensed in the presence of a Prescribing Program for LOTRONEX™ sticker, if generic substitution of alosetron is permitted pursuant to State substitution laws." Verified Complaint, Ex. 8, at 5 n. 1. This exception is critical, because it permits the dispensing of Roxane's product pursuant to prescriptions by healthcare providers that are ***not*** enrolled in the Roxane REMS. Verified Complaint ¶ 36.

This is problematic. 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: that LOTRONEX® only be dispensed pursuant to a prescription issued by a prescriber enrolled in the LOTROMEX® REMS. Verified Complaint ¶ 36. FDA reaffirmed this important requirement as necessary for the safe use of LOTRONEX® in 2008. *Id.* The requirement serves an important purpose: it ensures that Prometheus, through use of a database, can monitor the enrollment and compliance of prescribers in its program and undertake required efforts to ensure that REMS procedures are being followed properly (i.e., that prescribers are properly trained on the risks of the drug, that patients are receiving necessary information about how to monitor for problems, and that pharmacists are observing the procedural requirements imposed by the REMS). *Id.*

Because of the footnote mentioned above, Roxane's REMS does not offer this critical level of protection. Not having shared in its creation or management or contributed toward its costs (as likely would have been the case in a single, shared REMS), Roxane does not have access to the Prometheus database. *See* Verified Complaint ¶¶ 35-36. As a result, it has no mechanism for ensuring that prescribers are actually enrolled in the Prometheus program and/or

in compliance with its REMS requirements. *Id.* Similarly, Roxane will have no way to monitor and ensure that patients or prescribers are in compliance with the Roxane REMS. *Id.* And yet, the Roxane drug will be substituted by pharmacists to fill prescriptions written by Prometheus prescribers. 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 conditions. Verified Complaint, Ex. 8. The footnote in the Roxane REMS prohibits Roxane from carrying out the requirements in the Implementation System to monitor, evaluate and work to improve the REMS ETASU. For the same reason, the Roxane REMS will not ensure the same level of safe use of the Roxane product as the LOTRONEX® REMS.

The Roxane REMS is lacking a critical component of the LOTRONEX® REMS – an ironclad system pursuant to which the drug sponsor can ensure enrollment and compliance by prescribers. As such, the Roxane footnote renders the elements to assure safe use in Roxane's REMS not "comparable" to the Prometheus REMS.

II. THE PUBLIC INTEREST FAVORS THE REQUESTED RELIEF.

The public interest plainly favors granting an injunction here. Absent judicial intervention, FDA's actions will result in patients and providers being forced to navigate two separate REMS for alosetron hydrochloride. The additional costs and burdens on prescribers and pharmacists with complying with two sets of educational and safety materials, two different enrollment systems, two separate prescription verification systems, and two different adverse event reporting systems will lead to decreased quality of care for patients and is likely to lead some prescribers and patients to abandon alosetron hydrochloride in favor of treatments that are

less therapeutically effective for IBS-D. Verified Complaint ¶ 35. The result would be a decrease in effective treatment of patients with severe IBS-D or diminished prescriber compliance with REMS – each of which should weigh heavily in evaluating the public interest. *Id*. ¶ 35.

The public also has an unmistakable interest in seeing that laws are faithfully executed by public officials. *Fund for Animals, Inc. v. Espy*, 814 F. Supp. 142, 152 (D.D.C. 1993) ("there is a strong public interest in meticulous compliance with the law by public officials"); *see also, e.g., O'Donnell Constr. Co. v. District of Columbia*, 963 F.2d 420, 429 (D.C. Cir. 1992); *Nobby Lobby, Inc. v. City of Dallas*, 970 F.2d 82, 93 (5th Cir. 1992) (approving district court conclusion that "the public interest always is served when public officials act within the bounds of the law and respect the rights of the citizens they serve"). This public interest overrides any countervailing public interest in the availability of a cheaper purported generic drug. *See Mova Pharm. Corp.*, 140 F.3d at 1066 (upholding district court's decision that the public's interest in the "faithful application of the laws" tipped public interest prong in favor of requested preliminary injunction, notwithstanding the public's interest in the availability of generic drugs).

The public interest simply is not served by FDA capriciously forcing two separate administrative systems onto patients and the healthcare system simply because Roxane chose to drop out of negotiations for a single, shared REMS.

III. PROMETHEUS WILL SUFFER IRREPARABLE INJURY ABSENT IMMEDIATE RELIEF.

Unless enjoined by this Court, FDA's conduct will cause substantial, imminent, and irreparable injury to Prometheus. Roxane undoubtedly is poised to flood the market imminently.

Verified Complaint ¶ 5. Prometheus will, in turn, suffer severe irreparable harm, both reputational and commercial in nature.

First, Roxane's entry on the market with a separate REMS will cause irreparable reputational harm to Prometheus. The frustration, ill will, and increased costs experienced by prescribers, pharmacists, and patients in complying with two separate REMS will negatively affect Prometheus. Verified Complaint ¶ 40. These adverse effects on business reputation, goodwill, and relationships with prescribers and patients constitute irreparable harm sufficient to warrant injunctive relief. *Patriot, Inc. v. Dep't of Hous. and Urban Dev*., 963 F. Supp. 1, *5 (D.D.C. 1997) (asserting that damage to business reputation supports finding of irreparable harm); *see also Tate Access Floors v. Interface Architectural Res., Inc.*, 132 F. Supp. 2d 365, 378 (D. Md. 2001) (finding irreparable harm based in part on the "loss of long-term relationships with major customers, beyond the short-term loss of individual sales"), *aff'd*, 279 F.3d 1357 (Fed. Cir. 2002).

Second, entry of Roxane's drug into the market will have an immediate and precipitous effect on Prometheus' sales, market share, and pricing of LOTRONEX® – all of which will irreparably undermine Prometheus' ability to support existing product lines and invest in new ones. 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. Alonso Declaration ¶ 5. The impact on Prometheus would be commercially devastating. *Id.* ¶ 6. Sales of LOTRONEX® currently comprise over 25% of Prometheus' revenues, permitting the company to invest in promising new pharmaceutical and diagnostic products. *Id.* ¶ 6. There is no mechanism by which Prometheus can be made whole for the injury that would result from entry into the marketplace of Roxane's drug. And because the foregoing losses never can be

recovered from FDA, Prometheus will be irreparably harmed unless FDA's conduct is enjoined promptly.

It is well settled that these types of harm constitute irreparable harm sufficient to warrant a TRO. As this Court has explained, "[i]t is not at all difficult to foresee that [a pioneer drug company's] market position would collapse as soon as one or more generic drugs became available. [The innovator] would lose its head start in the market and its continued viability would be at issue. It could never recoup from FDA any losses that would occur. . . . These are the kinds of circumstances in which irreparable harm has been found." *CollaGenex Pharms., Inc. v. Thompson,* No. 03-1405 (RMC), 2003 WL 21697344, at *10 (D.D.C. July 22, 2003) (citing cases); *see also In re Cardizem Antitrust Litig.*, 200 F.R.D. 326, 340-41 (E.D. Mich. 2001) (describing predictable pattern of pioneer market share loss of up to 90% upon entry of competing generics); *Sanofi-Synthelabo v. Apotex, Inc.*, 488 F. Supp. 2d 317, 342-44 (S.D.N.Y. 2006) (describing sequence of events whereby generic drugs erode market share of pioneer drugs and noting that "irreversible price erosion . . . is a legitimate basis for a finding of irreparable harm"), *aff'd*, 470 F.3d 1368 (Fed. Cir. 2006); *Merrill Lynch, Pierce, Fenner & Smith, Inc. v. Bradley*, 756 F.2d 1048, 1054 (4th Cir. 1985) (noting that "customers cannot be unsolicited").

Because the foregoing losses can never be recovered from FDA, Prometheus will be irreparably harmed unless FDA's conduct is enjoined promptly. *See Bayer HealthCare, LLC v. U.S. Food and Drug Admin.*, 942 F.Supp.2d 17, 26 (D.D.C. 2013) (finding irreparable harm where the innovator drug company would "experience a decline in market share, price erosion, loss of customer good will, and loss of research and development funding as a result of [a generic's] entry into the market"). *See also Clarke v. Office of Fed. Hous. Enterprise Oversight,* 355 F. Supp. 2d 56, 65-66 (D.D.C. 2004) (holding that economic losses constitute irreparable

injury where they are unrecoverable due to government immunity); *Nat'l Med. Care, Inc. v. Shalala*, 1995 WL 465650, at *3 (D.D.C. June 6, 1995) ("[T]he policy considerations behind the judiciary's general reluctance to label economic injuries as 'irreparable' do not come into play in APA cases: even if the Plaintiffs ultimately prevail on the merits, they cannot bring an action to recover the costs of their compliance with the Defendant's unlawful retroactive rule, and thus will not be able to alleviate their economic damage through subsequent litigation."); *Woerner v. Small Bus. Admin.*, 739 F. Supp. 641, 650 (D.D.C. 1990) (finding irreparable injury where government is immune from damage suits to recover for economic losses); *Informatics Corp. v. United States*, 40 Fed. Cl. 508, 518 (1998) (finding irreparable harm where, absent the injunction, movant could recoup only the bid preparation costs and not lost profits).

IV. INJUNCTIVE RELIEF WILL NOT BURDEN DEFENDANTS' OR ROXANE'S LEGITIMATE INTERESTS.

Neither FDA nor Roxane can contend that it will be burdened if a TRO is issued, because neither has any legitimate interest in engaging in action that is contrary to the APA and the FDCA. Granting this motion would merely preserve the status quo by preventing Roxane's drug from overtaking the market pending further consideration by this Court. *See Anderson v. Davila*, 125 F.3d 148 (3d Cir. 1997); *Dist. 50, United Mine Workers v. International Union, United Mine Workers*, 412 F.2d 165, 168 (D.C. Cir. 1969) ("The usual role of [an] injunction is to preserve the *status quo*."). At worst, entry of a TRO would delay Roxane's entry into the generic market, but for good reason – to enable appropriate review of FDA's decision to waive the single shared REMS requirement that does not meet statutory standards for approval. It is particularly inappropriate in this case to permit Roxane to benefit from FDA's unlawful actions when Roxane chose to unilaterally withdraw from discussions regarding a single, shared REMS

despite Prometheus' continued attempts with Roxane and FDA to restart negotiations because a single shared REMS will benefit patients and the health care delivery system. Any resulting burden to Roxane of a TRO is far outweighed by the risk to patients, the health care delivery system, and Prometheus if injunctive relief is denied.

CONCLUSION

For all the foregoing reasons, Plaintiff's motion for a TRO and/or preliminary injunction should be granted.

Respectfully submitted,

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