IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

PROMETHEUS LABORATORIES, INC., Plaintiff, SYLVIA MATHEWS BURWELL, *et al*., Defendants.	Civil Action No. 1:15-CV-00742 (JEB)

FEDERAL DEFENDANTS' OPPOSITION TO PLAINTIFF'S MOTION FOR A TEMPORARY RESTRAINING ORDER AND/OR PRELIMINARY INJUNCTION

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I. INTRODUCTION

The question in this case is whether the Federal Food, Drug, and Cosmetic Act (the "FDCA") requires this Court to allow a drug manufacturer to single-handedly and indefinitely delay generic competition by refusing to agree to terms with a potential competitor on developing a common platform to ensure the continued safety of their marketed drug products.

Since 1938, FDA has been responsible for approving new drugs before they can be introduced into commerce. Over time, as markets and technology have evolved, Congress has expanded FDA's authority. In 1962, for example, Congress required FDA to determine that new drugs were not only safe, but also effective for their intended uses, before they could be marketed. In 1984, Congress passed new legislation intended to increase the availability to consumers of lower-cost generic medicines. And in 2007, Congress acted to enhance FDA's ability to ensure the continued safety of drugs after they had been approved.

Plaintiff Prometheus Laboratories Inc. ("Prometheus") acquired the rights in 2007 to Lotronex (alosetron hydrochloride), an already-approved drug that was subject to FDA's newly-enhanced postmarket safety authorities. There is no allegation that Prometheus has not faithfully adhered to its own obligations to ensure the safe use of Lotronex. The company has, however, been unable to successfully collaborate with Roxane Laboratories, Inc. ("Roxane"), the sponsor of an application to market a generic version of Lotronex, to establish a common platform (called a "single, shared system" under the FDCA) that both companies could employ to continue ensuring the safe use of all alosetron products. In large part because of this inability, FDA determined that the burdens of establishing a single, shared system outweighed the benefits, and granted Roxane's request to waive the single, shared system requirement. And after Roxane had

satisfied all of the other requirements for approval, FDA approved Roxane's application to market its alosetron product with a slightly different, though comparable, risk mitigation strategy.

Now, after dragging its feet for more than three years rather than collaborate with Roxane, Prometheus asks this Court to take immediate and extraordinary action to require FDA to rescind or stay its approval of Roxane's application, arguing that FDA has acted unlawfully by approving Roxane despite the absence of the single, shared system whose very development Prometheus itself blocked. But FDA carefully considered the statutory factors before granting Roxane's waiver request, and the conditions that FDA imposed when granting that waiver are well within its discretion in implementing the authority conferred by Congress. Prometheus will face generic competition inevitably, and its pretextual appeals to safety as a means to delay that competition fall flat. The fact that Prometheus does not like FDA's decision does not render that decision invalid. And no amount of gamesmanship by Prometheus can change the fact that the public interest is best served where, as here, the twin goals of increasing availability of lower-cost alternatives and ensuring the safety of marketed drugs are both advanced.

The Court should deny Prometheus's motion.

II. STATUTORY AND REGULATORY BACKGROUND

A. New Drug Applications And Abbreviated New Drug Applications

Under the FDCA, pharmaceutical companies seeking to market the initial version of a drug product (also known as the "innovator" or "pioneer" drug) must first obtain FDA approval by filing a new drug application ("NDA") containing extensive scientific data demonstrating the safety and effectiveness of the drug product. 21 U.S.C. § 355(a), (b). An NDA applicant must

also submit information on any patent that claims the drug, or a method of using the drug, for which a claim of patent infringement could reasonably be asserted against an unauthorized party. 21 U.S.C. § 355(b)(1), (c)(2). FDA publishes the patent information it receives in "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), *available at* http://www.fda.gov/cder/ob/. *See also* 21 U.S.C. § 355(j)(7); 21 C.F.R. § 314.53(e).

The Drug Price Competition and Patent Term Restoration Act of 1984 (the "Hatch-Waxman Amendments"), codified at 21 U.S.C. § 355 and 35 U.S.C. §§ 156, 271, and 282, permits manufacturers to submit abbreviated new drug applications ("ANDAs") requesting approval of generic versions of approved drug products. 21 U.S.C. § 355(j). The Hatch-Waxman Amendments were intended to balance encouraging innovation in new drug development with accelerating the availability to consumers of lower cost alternatives to such drugs. *See* H.R. Rep. No. 98-857 (Part I), 98th Cong., 2d Sess. at 14-15 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647-48; *see also, e.g.*, *Tri-Bio Labs., Inc. v. United States*, 836 F.2d 135, 139 (3d Cir. 1987).

ANDA applicants need not submit clinical data to demonstrate the safety and efficacy of the generic product, as is necessary with an NDA. Rather, an ANDA relies on FDA's findings that the previously-approved innovator drug (or "reference listed drug") is safe and effective. Specifically, under 21 U.S.C. § 355(j), the agency approves generics on the basis of chemistry, manufacturing, and bioequivalence data, among other required information, without evidence from literature or clinical data to establish effectiveness and safety. Under these provisions, if an ANDA applicant establishes that its proposed drug product has the same active ingredient(s), conditions of use, route of administration, dosage form, strength, and labeling as the reference

listed drug, and that it is bioequivalent[1] to that drug, the applicant can rely on the fact that FDA has previously found the reference listed drug to be safe and effective. The FDCA provides that FDA "shall approve" an ANDA "unless" the agency finds that one or more specified conditions is present. 21 U.S.C. § 355(j)(4); *see also* 21 C.F.R. § 314.127(a).

B. **Risk Evaluation and Mitigation Strategies (REMS)**

A primary goal of the Food and Drug Administration Amendments Act of 2007 ("FDAAA"), Pub. L. No. 110-85, was to "provide[ ] FDA with enhanced tools to ensure postmarket drug safety," and that law's risk evaluation and mitigation strategy ("REMS") provisions were "the centerpiece" of that effort. *See* H.R. Rep. No. 110-225, 110th Cong., 1st Sess. at 5, 12 (2007). In FDAAA, Congress authorized FDA to require applicants to submit a proposed REMS for a drug if FDA determines that doing so is necessary to ensure that the drug's benefits outweigh its risks. 21 U.S.C. § 355-1(a). FDA can require a REMS before a new drug application is initially approved or, if FDA becomes aware of new safety information and determines that a REMS is necessary, after an application has been approved. 21 U.S.C. § 355-1(a)(2), (b)(3). Before FDAAA was enacted, FDA had previously approved a small number of drugs and biologics with risk minimization action plans ("RiskMAPs"), strategic safety programs designed to meet specific goals and objectives in minimizing a drug's known risks while preserving its benefits.[2]

[1] Two drugs are considered bioequivalent if, in general, the rate and extent of absorption of the generic drug do not show a significant difference from the rate and extent of absorption of the listed drug. 21 U.S.C. § 355(j)(8)(B).

[2] Certain products were "deemed" to have an approved REMS in effect when FDAAA was enacted. FDAAA Section 909(b); 73 Fed. Reg. 16313 (Mar. 27, 2008).

A REMS is a required risk minimization strategy that can include one or more tools beyond routine professional labeling, such as a Medication Guide, a patient package insert, and/or a communication plan. *See* 21 U.S.C. §355-1(e). FDA also may require a REMS to include certain elements to assure safe use ("ETASU"). 21 U.S.C. § 355-1(f). The ETASU can include, for example, requirements that health care providers who prescribe the drug have particular training or experience, that patients using the drug be monitored, or that the drug be dispensed to patients with evidence or other documentation of safe use conditions. *See id.* Certain ETASU REMS may also include an implementation system through which the sponsor is required to monitor and evaluate implementation of the ETASU and work to improve their implementation. 21 U.S.C. § 355-1(f)(4).

C. **Generic Drugs and REMS**

Under the FDCA, a generic drug is subject only to certain elements of a reference listed drug's REMS. 21 U.S.C. § 355-1(i)(1). In particular, if the reference listed drug is subject to a REMS, an ANDA referencing that drug must have the same Medication Guide (if there is one) and the same or comparable ETASU. 21 U.S.C. § 355-1(i)(1)(A)-(B). Generally, the FDCA requires a generic drug and a listed drug to implement the ETASU through a single, shared system ("SSS"). *Id.* FDA can waive that requirement, however, and may permit the ANDA holder to use a "different, comparable aspect" of the ETASU if it determines that "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." *Id.*[3]

The FDCA prohibits the holder of an NDA covered by a REMS from using any ETASU "required . . . under this subsection to block or delay approval of an [ANDA] or to prevent application of such element under subsection (i)(1)(B) to a drug that is the subject of an [ANDA]" – *i.e.*, to a generic drug. 21 U.S.C. § 355-1(f)(8).

III. FACTUAL BACKGROUND

A. Lotronex

The NDA for Lotronex was originally owned by GlaxoSmithKline ("GSK"). FDA initially approved Lotronex in February 2000 for the treatment of irritable bowel syndrome (IBS) in women whose predominant bowel symptom was diarrhea. In November 2000, in response to postmarketing reports of ischemic colitis and serious complications of constipation and after discussions with FDA, GSK voluntarily withdrew Lotronex from the market. In June 2002, FDA approved a supplemental application for Lotronex with a RiskMAP to address the risks of ischemic colitis and serious complications of constipation associated with its use.

Under FDAAA, Lotronex was deemed to have in effect an approved REMS by virtue of the elements in its RiskMAP. In September 2008, Prometheus (which had acquired the rights to market Lotronex from GSK in 2007) submitted a proposed REMS for Lotronex, and FDA approved it in September 2010. The two goals of the Lotronex REMS (also known as the "Prescribing Program for Lotronex," or "PPL") are (1) to mitigate the risk of ischemic colitis and serious complications of constipation associated with Lotronex use by ensuring that Lotronex is

[3] FDA also may waive the SSS requirement if it makes a determination based on patent licensing or trade secret protection reasons that do not apply here. *See* 21 U.S.C. § 355-1(i)(1)(B)(ii).

used in only severely affected patients for whom the benefits exceed the risks, and (2) to ensure that the risks of ischemic colitis and serious complications of constipation associated with Lotronex use are communicated to patients, pharmacists, and prescribers. *See* Lotronex REMS, *available at* http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM227960.pdf, at 1.

The Lotronex REMS consists of a Medication Guide and several ETASU. The ETASU require (1) that healthcare providers who prescribe Lotronex are specially certified in the PPL; (2) that each patient for whom Lotronex is prescribed signs a Patient Acknowledgement Form ("PAF") documenting that certain safe use conditions are in place; and (3) that pharmacists dispense Lotronex only with documentation of certain safe use conditions. *Id.* at 2-5. In practice, implementation of the PPL means that, among other things:

- Healthcare providers, in order to obtain certification, must attest that they have read and understand the Lotronex prescribing information and other Lotronex REMS enrollment materials;
- Healthcare providers must ensure that patients are educated about the risks and benefits of Lotronex by reviewing the contents of the Medication Guide with patients and by having patients sign a PAF; and
- Healthcare providers must affix to written prescriptions for Lotronex PPL stickers showing that they are certified to write those prescriptions, and pharmacists may only dispense Lotronex if there is a written prescription with a PPL sticker (the "sticker requirement").

Id. The REMS also includes an implementation system, through which Prometheus evaluates and monitors compliance with its requirements, and a timetable for the submission of REMS assessments. *Id.* at 6.

Prometheus listed two patents for Lotronex; the first expired on January 13, 2013, and the second was held invalid by the United States District Court for the District of New Jersey on May 21, 2014.[4] *See* April 30, 2015 Memorandum from Dale Conner ("Waiver Memo") (attached as Exhibit 1) at 2. Lotronex is no longer subject to any form of statutory marketing exclusivity. *Id.*

B. Roxane's ANDA for Alosetron Hydrochloride and Efforts To Establish A Single, Shared System

Roxane submitted ANDA 20-0652 for alosetron hydrochloride (alosetron) tablets, 0.5 mg and 1.0 mg, and FDA received the ANDA on October 14, 2009. In a letter dated July 28, 2011, FDA notified Roxane that a REMS was required for this ANDA. In that letter, FDA also notified Roxane that a drug that is the subject of an ANDA and the listed drug that it references must use a single, shared system for ETASU unless FDA waives that requirement. FDA subsequently requested that Roxane contact Prometheus to discuss development of an SSS REMS.

Despite a substantial investment of time and energy over more than three years, Prometheus and Roxane were unable to develop an SSS. *See generally* Waiver Memo at 4-13. Discussions initially began in February 2012, *see id.* at 4, (b) (4)

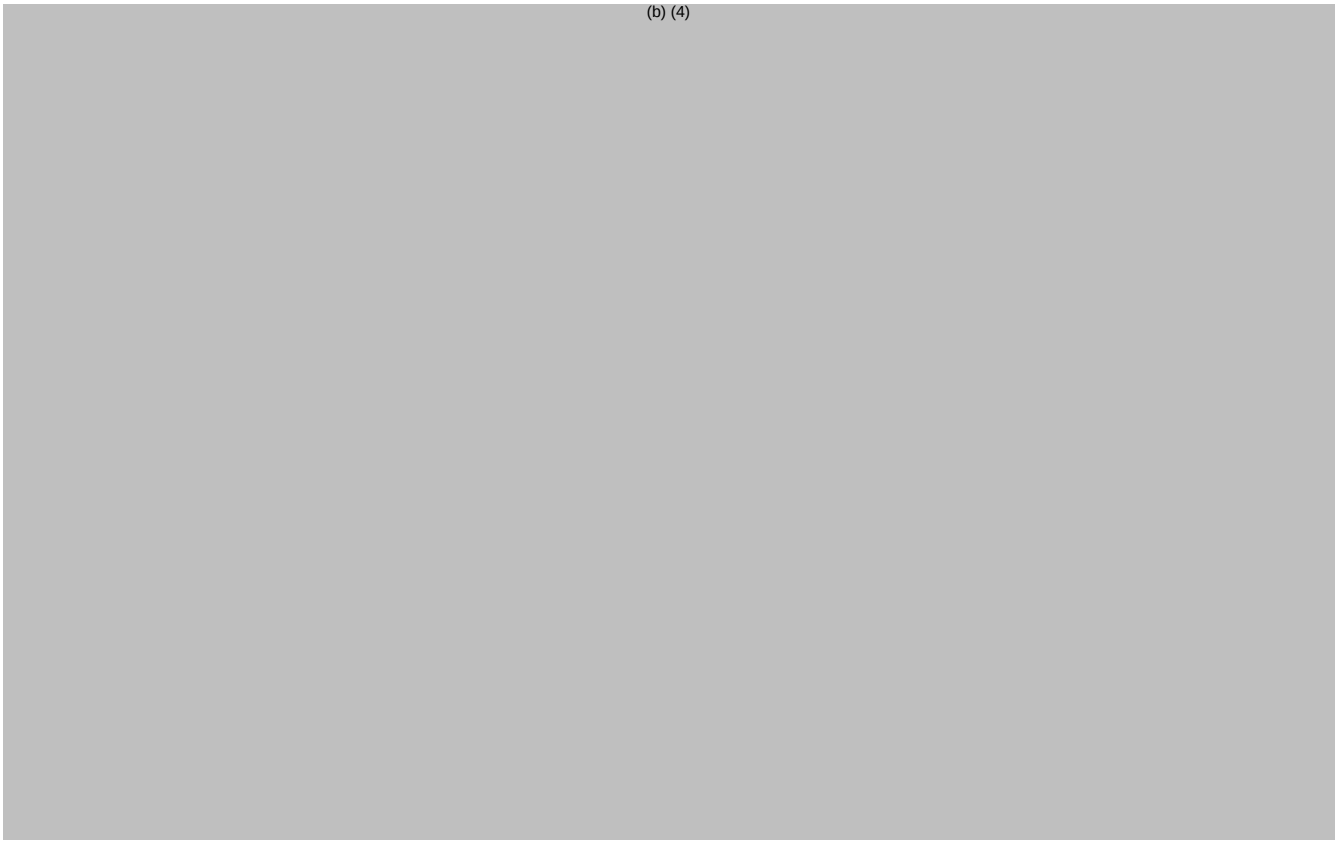
On March 15, 2013, Roxane requested that FDA waive the SSS requirement. *Id.*

In May 2013, Prometheus submitted a citizen petition to FDA, asking (1) for FDA to engage in notice and comment rulemaking to establish the standards and processes for single shared REMS and waivers from the SSS requirement, and (2) that it be given notice and the

[4] The District Court's ruling is currently under appeal.

opportunity to participate in any process used by FDA to determine whether to waive the SSS requirement for Lotronex. *See* Letter from W. Franzblau, Prometheus Laboratories Inc., FDA-2013-P-0572 (May 10, 2013). FDA responded to the citizen petition on October 7, 2013. *See* Letter from J. Woodcock, FDA, to W. Franzblau, Prometheus Laboratories Inc., FDA-2013-P-0572 (Oct. 7, 2013). FDA's response denied the request to engage in rulemaking at that time, but described the processes that shared system participants had used successfully in the past. *See id.* at 5-7. FDA also denied Prometheus's request that it be provided with notice of any SSS waiver requests submitted for Lotronex, but invited Prometheus to submit any information that it believed the agency should consider on the topic, and noted that FDA had invited Prometheus and Roxane to FDA to discuss the development of an SSS (including possibility of a waiver) for Lotronex. *Id.* at 7.

(b) (4)



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(b) (4)

On September 22, 2014, the REMS Oversight Committee in FDA's Center for Drug Evaluation and Research ("CDER") convened to discuss the ongoing negotiations and Roxane's request for a waiver, which by then had been pending for more than a year and a half. *Id.* at 15. The Committee expressed its concern that additional negotiations were unlikely to be successful, and that further efforts to require the parties to negotiate could unnecessarily delay approval of Roxane's ANDA. *Id.*

C. FDA's Decision To Grant A Waiver

On April 30, 2015, FDA determined that the standard for granting a waiver of the SSS requirement had been met with respect to Roxane's alosetron ANDA. *See id.* FDA observed that, while an SSS REMS for all alosetron products would have been ideal, the parties' inability to reach agreement after more than three years of discussions threatened to indefinitely delay approval of a generic alosetron product. *Id.* at 15-16. The agency reasoned that it lacked an effective mechanism to force the two parties to reach agreement, since the FDCA's enforcement authorities are designed to further FDA's public health mission and not to address anticompetitive behavior. *Id.* at 16.

FDA determined that, under the circumstances, a waiver was appropriate because the burden of creating an SSS was substantial in light of the impact on the sponsors (as illustrated by the protracted and unproductive discussions between Prometheus and Roxane) and on patients who were being deprived of access to generic alosetron. *Id.* FDA found that the ETASU in Roxane's proposed REMS were comparable to those in Prometheus's approved REMS, observing that the proposed REMS submitted by Roxane "mirrors the current Lotronex REMS." *Id.* In making this determination, FDA specifically considered the impacts of granting a waiver on health care providers, patients, the ANDA sponsor (Roxane), and the reference drug product holder (Prometheus). *Id.* at 17-18.

Finally, FDA attached two conditions to the waiver. *Id.* at 18. The first condition is that the waiver-granted REMS will be available to all current and future sponsors of ANDAs or NDAs for alosetron products. *Id.* This condition allows FDA to cap the number of REMS for alosetron products at two (Prometheus's REMS and the waiver-granted REMS), and the agency

expressed its intention to closely monitor compliance to ensure that no future ANDA sponsor is refused entry into Roxane's waiver-granted program. *Id.* at 19. The second condition is that the waiver will be for a three-year term that will expire absent further action. *Id.* at 18. FDA explained that this condition serves two purposes: first, it removes Prometheus's economic incentive to block generic competition, and second, it allows the agency to monitor the impact on stakeholders of having multiple REMS for a finite period of time. *Id.* at 19. FDA expressed its intention to evaluate the waiver's practical effects and determine whether to extend it or let it expire at the end of this three year period. *Id.*

FDA approved Roxane's ANDA on May 4, 2015, including approval of Roxane's proposed REMS. *See* May 4, 2015 Letter from Carol A. Holquist, FDA, to Roxane Laboratories, Inc. Neither Prometheus nor any other party has suggested that Roxane's ANDA did not meet the FDCA's standard for approval.

D. (b) (4)

[redacted]

(b) (4)

IV. ARGUMENT

Preliminary injunctive relief is an "extraordinary and drastic" remedy that "may only be awarded upon a clear showing that the plaintiff is entitled to such relief." *Winter v. NRDC, Inc.*, 555 U.S. 7, 20-26 (2008); *Munaf v. Geren*, 553 U.S. 674, 676 (2008); *see also Mpoy v. Fenty*, 674 F. Supp. 2d 163, 165 (D.D.C. 2009) ("Injunctive relief is an extraordinary remedy, and plaintiff bears a substantial burden to obtain it."). To obtain either a temporary restraining order or a preliminary injunction, a party must establish that: (1) it is likely to succeed on the merits; (2) it is likely to suffer irreparable harm in the absence of preliminary relief; (3) the balance of equities tips in its favor; and (4) an injunction would serve the public interest. *Winter*, 555 U.S. at 20; *see also Hall v. Johnson*, 599 F. Supp. 2d 1, 3 n.2 (D.D.C. 2009) (the same standard applies to both temporary restraining orders and preliminary injunctions).

It is "particularly important" for a movant to demonstrate likely success on the merits. *Astellas Pharma US, Inc., v. FDA*, 642 F. Supp. 2d 10, 16 (D.D.C. 2009) (absent "substantial indication" of likely success, there would be no justification for court's intrusion into ordinary

processes of administration and judicial review). Moreover, a party seeking preliminary injunctive relief must demonstrate an actual "likelihood" of success on the merits, not merely the existence of "questions so serious, substantial, difficult and doubtful, as to make them fair ground for litigation . . . ." *Munaf*, 553 U.S. at 690 (citations omitted). Nor is a mere "possibility" of irreparable harm sufficient to justify such relief:

> Our frequently reiterated standard requires plaintiffs seeking preliminary relief to demonstrate that irreparable injury is *likely* in the absence of an injunction. . . . Issuing a preliminary injunction based only on a possibility of irreparable harm is inconsistent with our characterization of injunctive relief as an extraordinary remedy that may only be awarded upon a clear showing that the plaintiff is entitled to such relief.

Winter, 555 U.S. at 22 (citations omitted, emphasis in original).

In this case, the burden on Prometheus is even higher, because it seeks not merely to preserve the *status quo*, but to obtain an order that would require FDA to immediately rescind or stay a lawful approval of a competitor's product where there is no dispute that the product met the requirements for approval. A court's power to issue such a mandatory injunction "should be sparingly exercised." *Mylan Pharms., Inc. v. Shalala*, 81 F. Supp. 2d 30, 36 (D.D.C. 2000). Prometheus has failed to meet its burden of demonstrating likely success on the merits or that it would suffer irreparable harm absent preliminary injunctive relief. Moreover, Prometheus's interest in delaying competition does not outweigh the interests of its generic competitors or the FDA's and the public's interest in approving safe and effective drug products with adequate assurances of postmarket safety. Accordingly, Prometheus's motion for a temporary restraining order and/or preliminary injunction should be denied.

A. Prometheus Is Not Likely To Succeed On The Merits

FDA's administrative decisions are subject to review under the Administrative Procedure Act ("APA"), and may be disturbed only if "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). This standard is highly deferential to the agency and heightened even further in cases involving scientific and technical decisions. *See Citizens to Preserve Overton Park, Inc. v. Volpe*, 401 U.S. 402, 416 (1971); *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1320 (D.C. Cir. 1998). The agency's administrative decision is also entitled to a presumption of validity. *See Fla. Power & Light Co. v. Lorion*, 470 U.S. 729, 743 (1985); *Camp v. Pitts*, 411 U.S. 138, 142 (1973). The reviewing court must determine whether the agency's decision was based upon consideration of the relevant factors and whether there has been a clear error of judgment. *See Overton Park*, 401 U.S. at 416. However, a reviewing court is "not empowered to substitute its judgment for that of the agency," *id.*, and must uphold the agency's action so long as it is "rational, based upon consideration of the relevant factors and within the scope of the authority delegated to the agency by the statute." *Motor Vehicle Mfrs. Ass'n, Inc. of U.S., v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 42 (1983).

1. FDA Properly Granted The Waiver To Roxane

There is no question of statutory construction in this case as it relates to FDA's authority to grant a waiver. The FDCA states unambiguously that FDA "may waive the requirement" of a single, shared system for a generic drug, "and permit the applicant to use a different, comparable aspect of the elements to assure safe use," after determining that "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). The only questions are therefore (1) whether FDA has determined that the burden of an SSS outweighs its benefit, after considering the impact on the four enumerated groups of stakeholders, and (2) whether the respective ETASU are "comparable."

FDA's decision memorandum expressly recited this standard, *see* Waiver Memo at 2-3, and it is beyond serious dispute that FDA's determination and analysis satisfies both statutory elements.

a. FDA Considered All Of The Relevant Factors

Prometheus alleges that "FDA has not made any showing" that the burden of creating an SSS outweighs the benefit, complaining that FDA's approval letter for Roxane's ANDA "failed to even attempt to explain how the burdens" outweighed the benefit. Plaintiffs' Memo at 14. This allegation completely lacks merit; FDA carefully examined all of the relevant factors. *See, e.g.*, Waiver Memo at 17 ("In accordance with Section 505-1(i)(1)(B), the Agency has also considered the impacts that granting a waiver . . . will have on health care providers, patients," Roxane, and Prometheus).[5]

There is no requirement that the agency must formulaically recite its consideration of each of these factors in all of its decisional memoranda. *See Bowman Transp., Inc. v. Arkansas-*

[5] Less than a week before filing its Complaint and moving for temporary injunctive relief, counsel for Prometheus submitted a Freedom of Information Act request to FDA in which it specifically asked for "FDA's decision memorandum supporting the decision to approve the Roxane alosetron REMS and waive the requirement for a single shared REMS for alosetron products." *See* Letter from L. Mehler, Hogan Lovells (May 12, 2015), attached as Exhibit 4. It is somewhat incongruous for Prometheus to complain that the agency had failed to set forth its rationale in one document, while simultaneously requesting a separate document that it apparently expected to contain the agency's rationale.

Best Freight Sys., Inc., 419 U.S. 281, 286 (1974) ("[W]e will uphold a decision of less than ideal clarity if the agency's path may reasonably be discerned."); *Pac. Nw. Newspaper Guild, Local 82 v. NLRB*, 877 F.2d 998, 1002 (D.C. Cir. 1989) ("We may approve a curt explanation if the path of the agency's reasoning is clear"). Here, FDA's consideration of the relevant factors is plainly discernible from the text of the decisional memorandum.

To be clear, FDA acknowledged the potential benefits of an SSS REMS. *See* Waiver Memo at 15 ("Although a SSS REMS for all alosetron products would be ideal . . ."); *id.* at 17 ("there are some benefits to be gained from a SSS REMS, particularly in the form of increased efficiencies"). But the agency also recognized that "it seems unlikely that these benefits will ever materialize given the inability of the parties to agree to SSS REMS terms," and that "there is little FDA can do to force the two sides to agree to particular terms." *Id.* at 16-17. In light of the parties' three years of fruitless negotiations, FDA concluded "that the burden of creating a SSS REMS in this instance appears to be insurmountably large." *Id.*

FDA also specifically addressed the impacts of a waiver on each of the four stakeholder groups referenced in the statute. With respect to health care providers, FDA acknowledged that a second REMS might create some confusion. *Id.* at 17. The agency addressed that confusion, however, by requiring that Roxane's REMS specify that the generic product may be dispensed upon the presentation of either a Lotronex PPL sticker or a generic sticker.[6] *Id.* Even though two REMS was not the preferred path, FDA does not share Prometheus's concern about health care providers' ability to implement two programs simultaneously since these two programs are

[6] FDA noted that Prometheus may request a modification of its own REMS so that Lotronex can similarly be dispensed upon the presentation of either sticker. Waiver Memo at 17 n.40. (b) (4) [redacted].

"nearly identical," and the agency concluded that the benefit of avoiding any inefficiencies through an SSS REMS did not outweigh the burden associated with keeping a generic product off the market. *Id.* at 17-18.

With respect to patients, FDA found that a waiver would benefit patients, primarily by permitting patient access to a more affordable generic alosetron product. In addition, because the two programs' respective ETASU were comparable, FDA determined that the two REMS programs "should be comparable . . . in terms of protecting patient safety." *Id.* at 18. FDA does not believe that the existence of two REMS would meaningfully compromise the clarity of the safety messages, or create the potential for a meaningful increase in medical errors. *Id.*

Finally, FDA determined that Roxane would "benefit significantly" from a waiver, while a waiver would have "virtually no impact on Prometheus." *Id.* Absent a waiver, Prometheus could "continue to effectively deny approval of [Roxane's] pending ANDA simply by prolonging the negotiations over a SSS REMS," and a waiver provided a means for Roxane's ANDA to come to market. *Id.* Conversely, a waiver would not affect either Prometheus's "ability to continue using its approved REMS," or "the cost of that REMS." *Id.* FDA concluded that any competitive harm suffered by Prometheus from the entry of generic competition was "the result intended under the Hatch Waxman amendments." *Id.*

Accordingly, and consistent with the statutory requirement, FDA determined "that the standard for granting a waiver of the SSS REMS requirement has been met with respect to Roxane's [ANDA] for alosetron because the burden of creating a SSS REMS in these circumstances outweighs the benefits of the SSS REMS." *Id.* at 1-2; *see also id.* at 16 (concluding "that the burden of creating a REMS for alosetron products outweighs the benefit of

a SSS REMS under the present factual circumstances."). The determination to grant a waiver was rational and was the product of FDA's consideration of all the relevant factors, and there is simply no basis for disturbing this decision.

b. Roxane's ETASU And Prometheus's ETASU Are Comparable

Prometheus acknowledges, as it must, that the two REMS do not need to be identical. *See* Plaintiffs' Memo at 16. Rather, the statute expressly provides that the respective REMS' ETASU may be "different," so long as they are "comparable." 21 U.S.C. § 355-1(i)(1)(B).

FDA, indeed, determined that the ETASU in Roxane's proposed REMS were comparable to those in the approved Prometheus REMS. *See* Waiver Memo at 16. The agency stated specifically that "because Roxane's proposed REMS was modeled after Prometheus' approved REMS, Roxane's proposed REMS has the same elements to assure safe use that are included in Prometheus' approved REMS. Roxane's proposed REMS is substantially similar to Prometheus' REMS in all other respects as well." *Id.* As even Prometheus admits, "both [ETASU] 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." Plaintiffs' Memo at 16-17.

Prometheus takes issue with one footnote in Roxane's REMS, which permits a pharmacist to dispense generic alosetron (if substitution is permitted under state law) upon presentation of a Lotronex PPL sticker. This difference is illusory, however, and does not negate the fact that the two ETASU are comparable. The substantive elements of the two REMS are, for all intents and purposes, identical: prescribers will receive the same training on the drugs, patients will receive the same information about the drugs, and pharmacists may not dispense the

drugs absent documentation of the prescribers' compliance. Thus, other than the drug's brand name, there is no meaningful difference in application of the two REMS from the perspective of patient safety. Prometheus's real complaint is that a generic alternative can be substituted for its product.

The relative insignificance of this difference is underscored by (b) (4) [redacted] Any difference (b) (4) [redacted], and under no circumstances does it justify the relief Prometheus seeks.

Nor can Prometheus credibly argue that the statute "unambiguously forbids" FDA's determination of comparability. Congress expressly provided that a second REMS could "use a different, comparable aspect" of the first REMS's ETASU. 21 U.S.C. § 355-1(i)(1)(B). Within the same section, Congress also specified that ETASU should "be designed to be compatible with established distribution, procurement, and dispensing systems for drugs," 21 U.S.C. § 355-1(f)((2)(D)(ii), and Congress prohibited the sponsor of a reference listed drug from using an ETASU "to block or delay approval of" a generic alternative "or to prevent application of such element under subsection (i)(1)(B)" to a generic alternative. 21 U.S.C. § 355-1(f)(8). Taken together, these provisions evidence a clear Congressional intent that REMS not be used either to impede the approval of generic alternatives or to interfere with common generic substitution practices.

2. FDA Is Authorized To Place Conditions On The Waiver

Prometheus argues that "the FDCA does not authorize the agency to impose non-statutory conditions in order to justify a waiver." Plaintiffs' Memo at 13; *see also id.* at 12 (asserting that FDA lacks "authority to attach conditions to grant a modified waiver in order to overcome an applicant's failure to meet the standard."). This argument is off the mark; FDA did not impose conditions in order to justify the waiver. Rather, as previously explained, FDA determined that Roxane satisfied the statutory requirements for a waiver. Once it determined that a waiver was appropriate, FDA then made the waiver conditional. *See, e.g.*, Waiver Memo at 18 (addressing waiver conditions after first determining that waiver was appropriate). This exercise of discretion was well within the scope of the agency's authority, and clearly permissible.

If the Court views this as a question of statutory interpretation, rather than a matter of how the agency applies its clear statutory authority, then the Court is governed by the familiar two-step analysis of *Chevron, U.S.A., Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837 (1984). Applying *Chevron*, the Court must ask first "whether Congress has directly spoken to the precise question at issue." 467 U.S. at 842. If, after this Court "exhaust[s] the 'traditional tools of statutory construction,'" *Natural Res. Def. Council, Inc. v. Browner*, 57 F.3d 1122, 1125 (D.C. Cir. 1995) (quoting *Chevron*, 467 U.S. 837, 843 n. 9), the intent of Congress is clear, "that is the end of the matter." *Chevron*, 467 U.S. at 842. Put another way, the Court must initially decide "whether the statute unambiguously forbids the Agency's interpretation." *Barnhart v. Walton*, 535 U.S. 212, 218 (2002).

The FDCA simply does not speak to the question of conditions: it says only that FDA "may waive the [SSS] requirement" upon making the required determination. 21 U.S.C. § 355-

1(i)(1)(B). It does not even impliedly forbid conditions, let alone unambiguously. Since the statute "is silent or ambiguous with respect to the specific issue," the Court proceeds to the second prong of *Chevron*, under which "the question for this court is whether the agency's answer is based on a permissible construction of the statute." *Chevron*, 467 U.S. at 843; *Cnty. of L.A. v. Shalala*, 192 F.3d 1005, 1012-13 (D.C. Cir. 1999). FDA's construction must be sustained as long as it is permissible, even if the Court might have adopted a different reading. *See Chevron*, 467 U.S. at 843-44 & n. 11; *Cnty. of L.A.*, 192 F.3d at 1012-13. The Supreme Court has "long recognized that considerable weight should be accorded to an executive department's construction of a statutory scheme it is entrusted to administer." *United States v. Mead Corp.*, 533 U.S. 218, 227-28 (2001); *see also Novartis Pharms. Corp. v. Leavitt*, 435 F.3d 344, 349 (D.C. Cir. 2006) ("We have held on a number of occasions that FDA interpretations of the FDCA receive deference.").

FDA's mission is to, among other things, protect the public health by helping to ensure that drug products are safe and effective. 21 U.S.C. § 393(b)(2)(B). Congress has vested FDA with authorities intended to accelerate the availability of lower-cost generic alternatives, *see* 21 U.S.C. § 355(j), and to ensure postmarket drug safety, *see* 21 U.S.C. § 355-1. The conditions that FDA imposed on Roxane's waiver here further both of those goals.

First, FDA stated that the waiver-granted REMS would be available to all current and future sponsors of applications to market alosetron hydrochloride products. The effect of this condition is to ensure that current and future applicants will not to develop their own separate REMS systems; instead, future applicants can utilize the program that Roxane developed and FDA approved. As FDA noted, the primary purpose of this condition is to facilitate the agency's

ability to cap the number of REMS for alosetron products at two, striking an appropriate balance between efficiency and the need to help ensure postmarket safety. *See* Waiver Memo at 19.

Second, FDA stated that the waiver would be for a three-year term that would expire without further action. As explained in the Waiver Memo, this condition "serves two purposes. First, it removes Prometheus' economic incentive not to agree to SSS terms to delay or block generic competition. Second, it creates a limited period of time during which the Agency can monitor the impact on stakeholders of having multiple alosetron REMS." *Id.* FDA further noted its intention to evaluate the waiver's effects, and determine whether it should be renewed, at the end of the three-year period. *Id.*

As the Supreme Court has stated:

> The power of an administrative agency to administer a congressionally created . . . program necessarily requires the formulation of policy and the making of rules to fill any gap left, implicitly or explicitly, by Congress. If Congress has explicitly left a gap for the agency to fill, there is an express delegation of authority to the agency to elucidate a specific provision of the statute by regulation. Such legislative regulations are given controlling weight unless they are arbitrary, capricious, or manifestly contrary to the statute. Sometimes the legislative delegation to an agency on a particular question is implicit rather than explicit. In such a case, a court may not substitute its own construction of a statutory provision for a reasonable interpretation made by the administrator of an agency.

Chevron, 467 U.S. at 843-44 (citation and quotation omitted). FDA's decisions to grant a waiver to Roxane, and to impose conditions upon that waiver, are unquestionably within the scope of the agency's authority, based upon consideration of the relevant factors, and rational, and they should be upheld. *Motor Vehicle Mfrs. Ass'n of U.S., Inc.*, 463 U.S. at 42.

B. Prometheus Has Not Shown That It Will Suffer Irreparable Injury Absent Relief

Prometheus claims that it will suffer harm, both reputational and commercial, in the event that this Court does not grant preliminary relief. The losses alleged by Prometheus are the inevitable consequence of the emergence of a generic into the marketplace – an event which Prometheus is powerless to prevent – and are insufficient to justify intervention.

Economic loss, in and of itself, generally does not constitute irreparable harm. *Wisc. Gas Co. v. Federal Energy Regulatory Commission*, 758 F.2d 669, 674 (D.C. Cir. 1985); *Mylan Pharm., Inc. v. Shalala*, 81 F. Supp. 2d at 42; *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212, 220 (D.D.C. 1996); *Varicon Int'l v. Office of Personnel Management*, 934 F. Supp. 440, 447 (D.D.C. 1996). Even irrecoverable economic loss does not rise to the level of irreparable harm unless the financial injury is "serious in terms of its effect on the plaintiff." *Gulf Oil Corp. v. Dep't of Energy*, 514 F. Supp. 1019, 1026 (D.D.C. 1981). "Irretrievable" monetary loss may constitute irreparable harm only if it is "so severe as to cause extreme hardship to the business or threaten its very existence." *Hi-Tech Pharmacal Co. v. FDA*, 587 F. Supp. 2d 1, 11 (D.D.C. 2008) (internal quotation marks omitted).

Prometheus's claimed irreparable harm is, in part, that Roxane's entry into the market will negatively impact its own sales, because it will no longer have the market for alosetron products to itself. But although Prometheus characterizes this effect as "commercially devastating," (Plaintiff's Memo at 20) it has not made any attempt to quantify its projected loss. Nor has Prometheus demonstrated that whatever loss in sales would result from the presence of a generic alternative on the market would cause it extreme hardship in the short period before this case is resolved on the merits, much less threaten the company's very existence. All brand name manufacturers know from the outset that the eventual approval of lower cost generics generally

leads to lower prices for consumers and to a corresponding loss of sales; this economic fact of life does not justify extraordinary injunctive relief. The Hatch-Waxman Amendments were intended to introduce such competition. *In re Barr Labs., Inc.*, 930 F.2d 72, 76 (D.C. Cir. 2006) (explaining that in enacting the Hatch-Waxman Amendments, "Congress sought to get generic drugs into the hands of patients at reasonable prices – fast"). And Prometheus, which acquired Lotronex more than seven years after FDA first approved the drug for marketing, could not reasonably have expected to hold a perpetual monopoly on alosetron products.

Perhaps more importantly, Roxane will enter the market, and Prometheus will experience the negative effect that it fears, even *if* this Court enters a preliminary injunction. It is not a question of whether, but when. Prometheus has no right to keep Roxane's, or any other generic alosetron product, out of the marketplace forever. FDA has found that Roxane's ANDA meets the requirements for approval, and approved it. Prometheus will have to face the loss of sales associated with the release of a generic, whether Roxane proceeds with a separate REMS or is forced to negotiate a single, shared REMS with Prometheus. Prometheus is cynically challenging FDA's decision as a means of further delaying Roxane's inevitable entry into the market for as long as possible.

Finally, it should be noted that FDA approved Roxane's ANDA on May 4, 2015. Prometheus waited two weeks, until May 18, 2015, to seek relief from this Court. Despite its insistence that immediate relief is warranted, Prometheus' delay in filing this action can and should be considered to weigh against its assertion that it will suffer irreparable harm in the absence of emergency injunctive relief. *See Mylan Pharms. Inc. v. Shalala*, 81 F. Supp. 2d at 43 ("Mylan's delay in bringing this action further undercuts its allegation of irreparable harm.").

C. The Balance Of Equities And The Public Interest Weigh Against Relief

FDA has no commercial stake in the outcome of this litigation, but the agency certainly has an interest in seeing its decisions effectuated. *See Mylan Labs., Inc. v. Henney*, 94 F. Supp. 2d 36, 59 (D.D.C. 2000) (the government has an "interest in giving immediate force to an agency's orders and an interest in the authority and finality of [an] agency decision."). FDA is charged with implementing the statutory scheme governing drug safety and approval in the manner outlined by Congress in the FDCA and, as the expert agency entrusted by Congress with the authority to interpret and apply the FDCA, FDA has a significant interest in the appropriate interpretation and application of its statutory scheme. *See Mylan Labs. Inc. v. Leavitt*, 484 F. Supp. 2d 109, 124 (D.D.C. 2007) ("A faithful and coherent interpretation of the FDCA and Hatch-Waxman outweighs the purely financial harm to these drug companies.").

Moreover, since FDA already has approved Roxane's application to market a generic alosetron product, any financial harm that Prometheus would incur in the absence of a preliminary injunction (which, as discussed above, Prometheus will incur eventually, in either case), will be matched, if not exceeded, by the financial harm that Roxane would suffer if it were deprived of its existing (and unchallenged) right to market during the period that the requested temporary restraining order or preliminary injunction would be in effect. *See Serono Labs. Inc.*, 158 F.3d at 1326 (finding in similar circumstances that the balance of harms "results roughly in a draw."); *Bristol-Myers*, 923 F. Supp. at 221 (noting that generic company had "endured a seven year process to obtain FDA approval" and that "the effect of an injunction [on the generic company] . . . would be dramatically greater" than the harm to plaintiff); *cf. Ark. Dairy Coop., Inc. v. USDA*, 576 F. Supp. 2d 147, 161 (D.D.C. 2008) (noting that any harm plaintiffs would

suffer absent preliminary injunctive relief would be offset by substantial harm to defendant-intervenors if injunction were granted).

With regard to the public interest at stake, there can be no question that the launch of a generic version of Lotronex would inure to the benefit of the American consumer, who would gain quicker access to less expensive prescription drugs. As discussed above, in enacting the Hatch-Waxman Amendments, "Congress sought to get generic drugs into the hands of patients at reasonable prices – fast." *In re Barr Labs., Inc.*, 930 F.2d at 76. Moreover, "the public has a well-recognized interest in receiving generic competition to brand-name drugs as soon as possible, and a delay in the marketing of [the generic] drug could easily be against the public interest in reduced prices." *Apotex Inc. v. FDA*, 508 F. Supp. 2d 78, 88 (D.D.C. 2007). As the Fourth Circuit noted, "in *Winter*, the Supreme Court emphasized the public interest requirement, stating, '[i]n exercising their sound discretion, courts of equity should pay particular regard for the public consequences in employing the extraordinary remedy of injunction.'" *The Real Truth About Obama, Inc. v. Federal Election Commission*, 575 F.3d 342, 347 (4th Cir. 2009) (quoting *Winter*, 555 U.S. at 24). This rings particularly true here where, as noted, there is no dispute that Roxane's alosetron product meets the statutory requirements for approval.

Prometheus asserts that the public has an interest in seeing that laws are faithfully executed by public officials. The parties agree on this point, and as discussed above, FDA has fulfilled its responsibility in this case, to determine that Roxane's generic version of Lotronex meets the requirements for approval, and to ensure its continued safety after approval. It is also part of FDA's responsibility, and within its discretion, to determine what constitutes a

comparable risk mitigation strategy, such that the introduction of generic Lotronex into the market will be safe for the public. Prometheus is in no position to question that determination.

V. **CONCLUSION**

For the foregoing reasons, Prometheus's motion for a temporary restraining order and/or preliminary injunction should be denied.

Respectfully submitted,

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