UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

PROMETHEUS LABORATORIES INC. Plaintiff, v. SYLVIA MATHEWS BURWELL, in her official capacity as Secretary of Health and Human Services, STEPHEN OSTROFF, M.D., in his official capacity as Acting Commissioner of Food and Drugs, Defendants, and ROXANE LABORATORIES, INC. Intervenor-Defendant.	Case No. 1:15-cv-00742-JEB

ROXANE LABORATORIES, INC.'S MEMORANDUM OF POINTS AND AUTHORITIES IN OPPOSITION TO MOTION FOR TEMPORARY RESTRAINING ORDER

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INTRODUCTION

During the past three years, plaintiff Prometheus Laboratories Inc. ("Prometheus") has reaped tens of millions of dollars in windfall profits by refusing to negotiate in good faith with Roxane Laboratories, Inc. ("RLI") over the development of a single, shared system of elements to assure the safe use of alosetron-based products ("ETASUs")—insisting on conditions FDA has rejected during prior negotiations over the development of shared ETASUs for other drugs; refusing to acknowledge (much less respond to) basic inquiries from RLI; and even demanding that RLI pay Prometheus *to enter* (rather than *maintain*) such a system of ETASUs, all in violation of the statutory requirement that no brand manufacturer may "use any [ETASU] … to block or delay approval of [a generic drug]." 21 U.S.C. § 355-1(f)(8). Now that Prometheus's patents covering Lotronex® can no longer block the approval of RLI's application, and with FDA having determined that RLI's generic version of Lotronex® meets all substantive requirements for approval, the Agency rightly determined that enough is enough: Faced with choosing between a world in which no generic product could enter the market due to Prometheus's obstructive conduct and one in which patients are given access to the safe use of RLI's generic alosetron products, fully assured through an independent system of ETASUs that mirror the ones FDA approved for Lotronex®, FDA approved RLI's product on May 4, 2015.

This lawsuit is Prometheus's last-ditch effort to extend its monopoly. Its principal argument is that FDA somehow lacked the "authority to attach conditions to a waiver of a single shared REMS." Prometheus Br. at 2. Nonsense. The statute

says nothing about what FDA can or cannot do after it releases an applicant from participating in a single, shared system of ETASUs, and there is nothing irrational about the so-called "conditions" FDA allegedly "attached" to the waiver here. The first "condition" simply indicates that FDA will revisit its initial waiver decision in three years' time, as the Agency always has the right to do. And the second "condition" simply says that RLI cannot do what Prometheus has done (and what the statute expressly bars companies from doing)—close its system off to other applicants and thereby choke competition. In any event, Prometheus has no standing to object to these conditions, which ultimately inure to its benefit (by allowing for the reconsideration of a waiver Prometheus obviously doesn't like, and ensuring that Prometheus can join RLI's system if it chooses).

Prometheus's other arguments run even further afield. Though Prometheus apparently disagrees with FDA's balancing of the costs and benefits of a waiver, the statute delegates that quintessential policy decision to the Agency and, not surprisingly, provides no judicially manageable standards against which to evaluate FDA's policy choice. To the extent this issue even is subject to judicial review, it thus is entitled to the highest degree of deference: It must be upheld so long as it was "'based on a consideration of the relevant factors'" and did not involve "'a clear error of judgment.'" *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983) (quoting *Bowman Transp., Inc. v. Arkansas-Best Freight Sys., Inc.*, 419 U.S. 281, 285 (1974)). Yet apart from making self-serving policy claims about the supposed costs of a waiver and benefits of a shared system

(which, to reiterate, Prometheus has for years refused to negotiate in good faith), Prometheus offers no credible basis for thinking that FDA failed to consider the relevant factors for approval or so clearly erred in weighing them that its decision is not susceptible to even a rational explanation.

Finally, Prometheus asserts that RLI's independent system of ETASUs is not "comparable" to Prometheus's system. But Prometheus elsewhere concedes that the core elements of RLI's FDA-approved system are indeed materially identical to the Lotronex® system's core elements; its *only* complaint is that FDA's decision would permit pharmacists to substitute RLI's "alosetron" product where physicians who concededly have received the training and education needed to safely prescribe alosetron-based products write a prescription for "Lotronex®." Prometheus's real complaint, then, is not with the comparability of RLI's ETASUs to Prometheus's ETASUs: It is with the ordinary operation of state generic substitution laws, which of course are the driver of Hatch-Waxman's remarkable success and the self-evident motivation for Congress's insistence that ETASUs may not be used to impede generic competition.

Prometheus's legal arguments are bad enough to doom its motion. But its equitable claims are even worse. Though it is well-settled that monetary injuries cannot ground injunctive relief unless they threaten the movant's existence, Prometheus has not even attempted to make such a showing—much less explained how FDA's approval of RLI's ANDA threatens to drive Prometheus out of business during the limited window in which a TRO lawfully can remain in effect. There is a

reason for that: Prometheus has had years to plan for FDA's approval of generic alosetron products, and indeed has amassed a treasure trove of ill-gotten profits by refusing to negotiate in good faith with RLI in a transparent effort to delay RLI's approval for the past three-plus years. Moreover, because Prometheus mounts no challenge to FDA's expert determination that RLI's ANDA meets all *scientific and medical* requirements for approval—and elsewhere claims (insincerely) that it stands ready and willing to enter a single, shared system of ETASUs that would comply with its view of the statute and thereby permit RLI to launch its product—Prometheus's injuries are best-described as *inevitable*, not *irreparable*.

The same cannot be said for RLI. RLI has the legal right to market its alosetron products in interstate commerce *today*, pursuant to a lawful FDA approval. Out of respect for this Court, the Company will not do so before the conclusion of tomorrow's hearing. But after weeks of intensive planning, its product is ready to ship; its customers are lined up and clamoring for deliveries under contracts RLI entered in reliance on FDA's approval decision; and every additional day that passes without a launch is one in which RLI *irreparably* will have lost its statutory right to do precisely what Congress intended: deliver safe and affordable generic versions of this widely-prescribed drug to consumers, who have been forced to pay inflated prices for more than a decade. The motion should be denied.

ABBREVIATED BACKGROUND

As the government's response brief explains in detail, the federal Food, Drug and Cosmetic Act ("FDCA") and associated FDA regulations establish a highly reticulated scheme for the submission, review, and approval of prescription drugs in this country, including products that require ETASUs. In an effort to ease the burden on the Court, RLI will not set out a full description of the relevant statutory and regulatory background here, but instead relies on the statutory and regulatory background section set forth in the government's brief.

As for the pertinent factual background, and again to ease the burden this Court faces given tomorrow's hearing, RLI is contemporaneously filing two declarations from company employees. *See* Decl. of Rick Peterman (May 20, 2015) ("Peterman Decl.") (attached as Exhibit A to Motion for Leave to File Under Seal); Decl. of David Dow (May 20, 2015) ("Dow Decl.") (attached as Exhibit B to Motion for Leave to File Under Seal). Taken together, those declarations articulate in detail the factual background surrounding RLI's submission of ANDA No. 200652 for generic alosetron; Prometheus's deliberate frustration of the parties' negotiations in connection with efforts to develop a single, shared system of ETASUs; and the significant adverse effects that granting Prometheus's motion would have on RLI's commercial marketing plans, contractual commitments, and business relationships. Rather than rehash those details here, and to preserve the time and resources of the Court, RLI hereby states that it is relying on and incorporating the Peterman and Dow Declarations as if fully set forth herein.

LEGAL STANDARD

To secure temporary injunctive relief, a plaintiff must establish "[1] that he is likely to succeed on the merits, [2] that he is likely to suffer irreparable harm in the absence of preliminary relief, [3] that the balance of equities tips in his favor, and [4] that an injunction is in the public interest." *Aamer v. Obama*, 742 F.3d 1023, 1038 (D.C. Cir. 2014) (citing *Sherley v. Sebelius*, 644 F.3d 388, 392 (D.C. Cir. 2011), in turn quoting *Winter v. Natural Res. Def. Council, Inc.*, 555 U.S. 7, 20 (2008)). The movant must carry its burden of persuasion by a clear showing, *see Mazurek v. Armstrong*, 520 U.S. 968, 972 (1997) (per curiam), and that standard applies to *each* of the four factors: "The D.C. Circuit has further instructed that 'the movant has the burden to show that *all four factors* … weigh in favor of the injunction.'" *Holmes v. FEC*, __ F. Supp. 3d __, 2014 WL 5316216, at *3 (D.D.C. Oct. 20, 2014) (emphasis added) (ellipses in original) (quoting *Davis v. Pension Benefit Guar. Corp.*, 571 F.3d 1288, 1292 (D.C. Cir. 2009)).

ARGUMENT

I. PROMETHEUS HAS NO LIKELIHOOD OF SUCCESS ON THE MERITS.

A. Judicial Review Of FDA's Decision Is Subject To Cascading Layers Of Deference.

Judicial review of FDA's decision to approve RLI's ANDA is both sharply circumscribed and highly deferential. To the extent Prometheus challenges FDA's interpretation of the Hatch-Waxman Act (as it does in contesting the legality of the "conditions" FDA allegedly imposed when it released RLI from participating in a single, shared system of ETASUs that Prometheus for years refused to negotiate in

good faith), this Court is bound to uphold FDA's interpretation so long as it is not directly at odds with "the unambiguously expressed intent of Congress." *Chevron, U.S.A., Inc. v. NRDC*, 467 U.S. 837, 842-43 (1984). As a result, in cases where "Congress has not directly addressed the precise question at issue," the only question for the reviewing court "is whether the agency's answer is based on a permissible construction of the statute." *Id.* at 843. That limited inquiry does not involve a search for the "best" interpretation or even a "better" interpretation of the law: "Under the *Chevron* analysis, [courts] defer to an agency's interpretation, not only where it is the best interpretation, but where it is merely 'reasonable.'" *Grunewald v. Jarvis*, 776 F.3d 893, 900 (D.C. Cir. 2005) (quoting *Chevron*, 467 U.S. at 844).

That standard is generous, and as set forth below, FDA's interpretation of the statute easily passes muster. But it bears special emphasis here that Prometheus's other challenges must surmount an even greater degree of judicial deference to FDA's decisionmaking. In contrast to its interpretive challenge, Prometheus's other challenges do not contest FDA's interpretation of the statute: They challenge the Agency's cost-benefit analysis, which is a quintessential *policymaking decision* expressly vested in the Agency by the statute, and the safety of RLI's ETASUs, which likewise hinges on the exercise of FDA's *practical and scientific expertise* pursuant to an explicit statutory grant of authority.

As a result, the relevant question for those challenges is not whether FDA's decision was *reasonable*; instead, it is whether the Agency's decision was "*rational*,

based on consideration of the relevant factors and within the scope of the authority delegated to the agency by the statute." *State Farm*, 463 U.S. at 42 (emphasis added). It is hard to overstate the narrowness of that inquiry. As the Supreme Court has explained, an agency's decision will fail that test only "if the agency has relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise." *Id.* at 43. As set forth below, Prometheus's arguments do not remotely overcome the cascading layers of deference to which FDA's decision is subject.

B. The Statute's Plain Language Does Not Foreclose The "Conditions" Allegedly Attached To RLI's Waiver, And Those "Conditions" Are Eminently Reasonable.

Given the distinct standards that apply to its challenges, it is no surprise that Prometheus's lead argument purports to focus on the statutory text rather than the discretionary policy decisions Congress delegated to FDA. To that end, Prometheus asserts that "[t]he plain language of the statute does not grant FDA the authority to attach conditions to a waiver." Prometheus Br. at 12; *id.* at 13 ("[T]he FDCA does not authorize the agency to impose non-statutory conditions."). But that assertion does not address the proper question, which instead is whether the statute *unambiguously bars* FDA from imposing the two purported "conditions" Prometheus claims FDA unlawfully imposed here.

The statute does no such thing. Though it authorizes FDA to "waive the requirement [that a generic applicant participate in a shared system of ETASUs],

and permit the applicant to use a different, comparable aspect of the [ETASUs]" in certain circumstances, 21 U.S.C. § 355-1(i)(1)(B), the statute does not say anything about what FDA can or cannot do *after* it determines, in the exercise of its expressly-delegated policymaking authority, that those circumstances are present. Nor does anything in the statute unambiguously foreclose FDA from directing generic applicants who have received such a waiver to open their FDA-approved ETASUs to other companies or compel FDA to maintain a waiver for all time once it has been granted.

Given the statute's silence on "the precise question at issue," *Chevron*, 467 U.S. at 843, the Agency's decision warrants considerable deference: "If the agency's reading fills a gap … in a reasonable way in light of the Legislature's design, we give that reading controlling weight.'" *Regions Hosp. v. Shalala*, 522 U.S. 448, 457 (1998). That is so because Congress's silence represents an implied delegation of authority to the expert agency which must administer the law in light of its practical experience. *Chevron*, 467 U.S. at 843-44. Courts thus are barred from "'disturb[ing the Agency's decision] unless it appears from the statute or its legislative history that the [Agency's decision] is not one that Congress would have sanctioned.'" *Id.* at 845 (quoting *United States v. Shimer*, 367 U.S. 374, 382-83 (1961)).

Prometheus makes no attempt to meet that standard, because it could not possibly do so. The first supposed "condition" FDA imposed simply seeks to ensure that RLI does not do what Prometheus has done here—effectively close its ETASUs

to other applicants by refusing to negotiate other applicants' entry into that system in good faith. And it is fully consistent with the statute. After all, when Congress crafted the statutory provisions that govern ETASUs, it recognized that application holders facing the loss of their monopoly might be tempted to undertake the same anticompetitive actions Prometheus did here, and so expressly provided that:

> No holder of an approved covered application shall use any [ETASU] required by the Secretary under this subsection to block or delay approval of an application under [21 U.S.C. §§] 355(b)(2) or (j) … or to prevent application of such element under [21 U.S.C. § 355-1](i)(1)(B) to a drug that is the subject of an abbreviated new drug application.

21 U.S.C. § 355-1(f)(8). Moreover, Congress went on to define the term "covered application" to expressly include generic applications like RLI's alosetron application, *see id.* § 355-1(b)(2) (cross-referencing *id.* § 355(p)(1)(A)), thereby manifesting a clear legislative intent to bar generic applicants who receive a waiver from using their FDA-approved ETASUs to thwart other applicants' entry into the market. Against this backdrop, FDA's requirement that RLI not manipulate its FDA-approved ETASUs to stave off competitors not only is a permissible choice; it is virtually compelled by the statute, and so hardly can be deemed "contrary to clear congressional intent." *Chevron*, 467 U.S. at 843 n.9.

Nor is there any merit to Prometheus's challenge to the second putative "condition" FDA imposed: that (in Prometheus's words) "the waiver is limited to a term of three years." Prometheus Br. at 12. That is not what FDA said or did, and there would be nothing wrong with it if Prometheus's characterization was accurate. Instead, FDA's approval letter simply explained the initial term of RLI's waiver would last at least three years, and that "[i]f, at the end of the three-year

period, Roxane seeks to continue marketing pursuant to the waiver, the Agency will evaluate whether an extension of the waiver is appropriate at that time." Verified Compl., Ex. 7 at 3. In other words, FDA simply made clear that it intends to reevaluate its current decision in light of real-world experience with RLI's ETASUs in a few years' time—something FDA *always* has the power to do in light of potentially-evolving facts and circumstances. *See, e.g.*, 21 C.F.R. § 10.25(b) ("The Commissioner may initiate a proceeding to issue, amend, or revoke a regulation or order or take or refrain from taking any other form of administrative action."); *id.* § 10.33(a) ("The Commissioner may at any time reconsider a matter, on the Commissioner's own initiative or on the petition of an interested person.").

Needless to say, nothing in the FDCA's ETASU provisions remotely purports to abrogate FDA's longstanding authority to revisit its prior decisions in light of changed circumstances or compels FDA to maintain a waiver, once granted, for all time. Nor is it even clear that Prometheus has standing to challenge FDA's stated intention to revisit RLI's waiver in the future "[i]f … Roxane seeks to continue marketing pursuant to the waiver." Verified Compl., Ex. 7 at 3. Given Prometheus's evident disagreement with FDA's decision to grant such a waiver, it should *welcome* FDA's openness to possible future reconsideration of that decision—not *challenge* it. The fact that Prometheus is taking the opposite position here only confirms the insincerity of its challenge.

At bottom, Prometheus thus has not remotely made the requisite clear showing that it is likely to succeed on the merits.

C. To The Extent It Even Is Reviewable, FDA's Policy Decision To Grant RLI A Waiver Is Rational.

Prometheus next asserts that FDA's decision is arbitrary because the Agency allegedly failed to demonstrate that "the burden of creating a single, shared system … outweigh[s] the benefits to the health care system." Prometheus Br. 13 (citation omitted). Yet that argument categorically differs from Prometheus's principal claim: Rather than contest FDA's interpretation of the statute's language, this argument challenges FDA's cost-benefit analysis—a paradigmatic policy determination that Congress expressly delegated to the Agency, *see* 21 U.S.C. § 355-1(i)(1)(B)(1), and for which Congress supplied no judicially manageable standards against which to gauge the exercise of FDA's discretionary decisionmaking. The statute's silence on that score makes good sense: After all, the courts long have recognized that such policy decisions are best left to expert agencies, not federal courts. *United Parcel Serv., Inc. v. NLRB*, 92 F.3d 1221, 1225 (D.C. Cir. 1996) (citing *Chevron*, 467 U.S. at 865-66); *see also Pension Benefit Guar. Corp. v. LTV Corp.*, 496 U.S. 633, 651-52 (1990).

Given the express statutory delegation to FDA and the nature of its decisionmaking, this Court's inquiry into whether FDA's burden-benefit analysis was arbitrary is exceedingly narrow. As the Supreme Court explained in *State Farm*, the only question for the Court in such cases is "whether [FDA's] decision was based on a consideration of the relevant factors and whether there has been a clear error of judgment." 463 U.S. at 43 (citation and internal quotation marks omitted); *see also Ctr. for Auto Safety v. Peck*, 751 F.2d 1336, 1342 (D.C. Cir. 1985)

(explaining that "'a court is not to substitute its judgment for that of the agency'" and observing that "'cost-benefit analyses epitomize the types of decisions that are most appropriately entrusted to the expertise of an agency'") (quoting *State Farm*, 463 U.S. 29 & *Office of Commc'n of the United Church of Christ v. FCC*, 707 F.2d 1413, 1440 (D.C. Cir. 1983)); *see also Ass'n of Irritated Residents v. EPA*, 494 F.3d 1027, 1035 (D.C. Cir. 2007) (noting that where "decisions by the FDA involve a complex balancing of an agency's priorities, informed by judgments 'peculiarly within its expertise,' [the agency's decisions] are therefore ill-suited for judicial review") (citations omitted).

That standard forecloses any likelihood that Prometheus can succeed in this challenge. Though Prometheus' brief claims that FDA's approval letter for RLI's alosetron product "fail[s] to even attempt to explain how the burdens of creating a single, shared system outweighed the benefit of a single shared REMS," Prometheus Br. at 14, that approval letter is not the appropriate place to look for the Agency's cost-benefit analysis (and so is not designed to provide that analysis). Instead, as counsel for Prometheus acknowledged on Monday's status call and counsel for the Federal Defendants explained, the Agency has prepared a separate, stand-alone memorandum that fully details the cost-benefit analysis it conducted pursuant to the statute; that the Agency relied upon to justify the approval of RLI's waiver; and that we understand FDA intends to file contemporaneously with its response brief today.

Prometheus's related contention that the RLI approval letter likewise "failed to respond to any of the significant concerns expressed in" two letters submitted by Prometheus, Prometheus Br. at 14, fails for the same reason. FDA is not in the business of addressing concerns raised by one company (Prometheus) in a letter to another company (RLI); it does so in a detailed internal memorandum that becomes part of its Administrative Record, and again, we understand that FDA is filing that memorandum today. Put simply, Prometheus has not remotely shown it is likely to succeed on the merits of its claim that FDA failed to "consider[] the relevant factors" or that it made "a clear error of judgment" in making a determination that Congress expressly delegated to its expertise, because—by its own admission—Prometheus has no basis for making such claims. This argument can and should be rejected for that reason alone.

Without any basis for challenging FDA's actual cost-benefit analysis, Prometheus ultimately mounts an array of policy arguments that it believes support the benefits of a single, shared system and downplay its costs. Prometheus Br. at 14-16. But the fact that Prometheus disagrees with the outcome of a cost-benefit analysis it has never seen is no license for this Court to set aside a policy determination that the courts long have recognized the judiciary is ill-equipped to second-guess, *see, e.g.*, *Peck*, 751 F.2d at 1342—and not least of all because Prometheus's self-serving claims fail to address or acknowledge its sustained attempts, over nearly three years, to thwart generic market entry by refusing to negotiate in good-faith over the development and implementation of a single, shared

system of ETASUs, as detailed in the Dow Declaration. *See* Dow Decl. ¶¶ 10-36. At the end of the day, Prometheus's own misconduct put FDA in a bind: demand a single, shared system of ETASUs and, given Prometheus's proven record of anticompetitive conduct, thereby burden the healthcare system, generic applicants, and patients by preventing generic market entry entirely; or allow for the development of parallel systems that would enable generic market entry; ensure that all alosetron products can be safely delivered to patients who are clamoring for affordable alternatives to Lotronex®; and thereby fulfill Hatch-Waxman's promise. Prometheus obviously would prefer the former choice; FDA rationally made the latter choice; and there is no basis for this Court to second-guess that determination.

D. FDA Reasonably Concluded That Roxane's ETASUs Are Comparable To The Lotronex® ETASUs.

Finally, Prometheus purports to challenge FDA's determination that Roxane's ETASUs are sufficiently "comparable" to the ones in place for Lotronex® to ensure the safe use of these products. Prometheus Br. at 16-18. As with Prometheus's challenge to FDA's cost-benefit analysis, this challenge likewise disputes a quintessential policy decision for which there are no judicially manageable standards. Indeed, it contests FDA's expert medical and scientific judgment that RLI's FDA-approved ETASUs are sufficient to ensure the safe use of alosetron products—precisely the type of decision where deference to the Agency is at its apex. *See, e.g.*, *Rempfer v. Sharfstein*, 583 F.3d 860, 867 (D.C. Cir. 2009) ("FDA's contrary determination is a scientific judgment within its area of expertise,

the kind of judgment to which this court gives a high level of deference.") (citations and internal quotation marks omitted); *Schering Corp. v. FDA*, 51 F.3d 390, 399 (3d Cir. 1995) (holding that FDA's "judgments as to what is required to ascertain the safety and efficacy of drugs fall squarely within the ambit of the FDA's expertise and merit deference from us"). RLI respectfully submits that the Court should decline Prometheus's invitation to wade into this public-health dispute by second-guessing whether the comprehensive system of ETASUs FDA approved for RLI passes muster under an *ad hoc* set of standards that Prometheus never defines.

Indeed, the contours of Prometheus's challenge highlight its problematic nature. Prometheus's brief expressly concedes that the principal elements of the respective ETASUs for Lotronex®, on one hand, and RLI's alosetron products, on the other, are indeed virtually indistinguishable—requiring comparable prescriber education programs; the delivery of comparable information to patients; and comparable confirmation that prescribers are enrolled in an approved system of ETASUs before a prescription for alosetron or Lotronex® can be filled. Prometheus Br. at 16-17. According to Prometheus, however, the *only* defect in the FDA-approved ETASUs for RLI's product is *a single footnote* in a series of documents that *total hundreds of pages* and include *dozens of requirements*, and through which FDA has sought to fulfill Hatch-Waxman's mandate by accommodating state generic substitution laws, *id*. at 17—the network of statutes and regulations that are directly responsible for Hatch-Waxman's remarkable success in lowering prescription drug prices, because they permit pharmacists to dispense an FDA-

approved generic drug (*e.g.*, RLI's alosetron) where a given prescriber writes a prescription for the product's brand-name equivalent (*e.g.*, Lotronex®).

Despite the overwhelming overlap between the RLI program and the Lotronex® program, however, Prometheus's argument seems to be that this single footnote is *so important* that it renders the two programs wholly *non*-comparable. But Prometheus: offers no discernable standard for measuring the relative importance of this issue in the overall context of these extensive programs; provides no basis for assuming that FDA failed to consider the relative importance of this issue in the overall context of these extensive programs; makes no claim that FDA somehow was barred from considering generic substitution in light of the Hatch-Waxman Act's purposes and objectives, including the waiver provisions that Congress designed precisely to enable generic entry—and generic substitution—where brand manufacturers like Prometheus abuse ETASUs; and gives no reason to think that FDA acted irrationally in concluding that generic substitution at the pharmacy level will not adversely impact the overall safety of these two programs—which, to reiterate, *each* require that *any* doctor who writes *any* prescription for *any* alosetron product is enrolled in a registered program; receives appropriate training; supplies appropriate information to their patients; and can be monitored for compliance with the *admittedly* indistinguishable terms and requirements of these two programs.

As a result, Prometheus's challenge only confirms why the scope of judicial review in these cases is so limited: These kinds of decisions belong to the expert

agency Congress vested with the responsibility for evaluating the safety of drug products and determining the conditions under which they may enter interstate commerce, not the federal courts. Prometheus has not remotely overcome the extraordinary deference to which FDA's public-health determination is based, and cannot show that it is likely to succeed on the merits of its claim that FDA's decision is patently irrational.

II. PROMETHEUS HAS NOT MET THE EQUITABLE REQUIREMENTS FOR INJUNCTIVE RELIEF.

A. Prometheus Has Not Shown A Likelihood That It Will Suffer Irreparable Injury In The Absence Of The Requested TRO.

Prometheus not only has failed to show any likelihood of success on the merits; it has not made a "*a clear showing* 'that irreparable injury is *likely* in the absence of an injunction.'" *Dorsey v. District of Columbia*, 711 F. Supp. 2d 133, 135 (D.D.C. 2010) (quoting *Winter*, 555 U.S. at 22, itself citing *Mazurek*, 520 U.S. at 972) (first emphasis added). Indeed, the fact that Prometheus sat on its hands for two weeks before filing its so-called "emergency" motion belies any claim that it would suffer irreparable harm in the absence of such relief, and instead demonstrates that Prometheus calculated its actions to cause maximum disruption to RLI's commercial plans. *See, e.g.*, *Sandoz, Inc. v. FDA*, 439 F. Supp. 2d 26, 31 (D.D.C. 2006) ("Sandoz delayed pursuing this action until the last minute. The Supreme Court recently reiterated that a 'court considering a stay must also apply a strong equitable presumption against the grant of a stay where a claim could have been brought at such a time as to allow consideration of the merits without requiring entry of a stay.' Indeed, the 'last-minute nature of an application' or an applicant's

'attempt at manipulation' of the judicial process is grounds for denial of a stay, in and of itself.") (quoting *Hill v. McDonough*, 547 U.S. 573, 584 (2006) (further quotation omitted); *Gomez v. United States Dist. Court for the N. Dist. of Cal.*, 503 U.S. 653, 654 (1992) (per curiam)), *aff'd*, 2006 WL 2591087 (D.C. Cir. Aug. 30, 2006) (per curiam).

In any event, the principal "injuries" Prometheus asserts are the supposed monetary losses it will suffer from generic competition, and "[i]t is … well settled that economic loss does not, in and of itself, constitute irreparable harm.… 'The key word in this consideration is *irreparable*. Mere injuries, however substantial, in terms of money, time and energy … are not enough.'" *Wisconsin Gas Co. v. FERC*, 758 F.2d 669, 674 (D.C. Cir. 1985) (per curiam) (quoting *Virginia Petrol. Jobbers Ass'n v. FPC*, 259 F.2d 921, 925 (D.C. Cir. 1958) (per curiam)) (emphasis in original); *see also Biovail Corp. v. FDA*, 448 F. Supp. 2d 154, 164 (D.D.C. 2006) ("[T]he fact that the plaintiff will face competition in the market and may lose profits if the defendant approves generic Wellbutrin XL is insufficient to establish irreparable harm.") (citation omitted); *Mylan Pharm., Inc. v. Shalala*, 81 F. Supp. 2d 30, 42-43 (D.D.C. 2000); *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212, 220 (D.D.C. 1996). The only exception to that well-settled rule is where monetary losses would be be so severe that they "threaten[] the very existence of the movant's business." *Wis. Gas Co.*, 758 F.2d at 674; *ConverDyn v. Moniz*, __ F. Supp. 3d __, 2014 WL 4477555, at *9 (D.D.C. Sept. 12, 2014) (holding that "the mere fact that economic losses may be unrecoverable does not, in and of itself, compel a finding of

irreparable harm") (citing, *inter alia*, *Chaplaincy of Full Gospel Churches v. England*, 454 F.3d 290, 297 (D.C. Cir. 2006)); *see also Astellas Pharma US, Inc. v. FDA*, 642 F. Supp. 2d 10, 22 (D.D.C. 2009); *Coalition for Common Sense in Gov't Procurement v. United States*, 576 F. Supp. 2d 162, 168-69 (D.D.C. 2008); *Sandoz, Inc.*, 439 F. Supp. 2d at 32; *Sociedad Anonima Viña Santa Rita v. Dep't of Treasury*, 193 F. Supp. 2d 6, 14 (D.D.C. 2001).

But Prometheus makes no serious effort to demonstrate how sales of RLI's generic alosetron products would imperil Prometheus's very existence, much less how FDA's approval of RLI's ANDA could do so during the truncated time period in which a TRO could remain in effect. To the contrary, Prometheus has had years to plan for the approval of generic alosetron products, and admits that Lotronex® generates just "25% of Prometheus' revenues." Prometheus Br. at 20. That is hardly enough to drive the company out of business in the next few weeks, and pales in comparison to the harms asserted in the cases Prometheus invokes. Take *CollaGenex Pharmaceuticals, Inc. v. Thompson*, 2003 WL 21697344 (D.D.C. 2003). In that case, the plaintiff:

- relied on the product at issue for nearly its entire revenue stream—ranging from "95%, 84-87%, and 82%" of total revenues during the relevant time period—such that competition *actually would imperil the company's continued existence*;
- had operated on a net loss for years—such that competition *unquestionably would have sent the company into economic ruin*; and
- was a stand-alone company that employed a mere 150 people total—such that competition *actually would threaten the company's entire workforce*.

Id. at *3.

Suffice it to say, Prometheus's asserted injuries do not remotely reach that cataclysmic level. Though it may lose some portion of future profits, that is simply the result Congress expected to follow from the ordinary operation of the Hatch-Waxman scheme—and it is a result the courts repeatedly have held insufficient to warrant injunctive relief. *See, e.g.*, *Astellas Pharma*, 642 F. Supp. 2d at 21-23 (holding that loss of "approximately half" of brand's total domestic revenue not enough to demonstrate irreparable injury); *Bristol-Myers Squibb Co.*, 923 F. Supp. at 221 (holding that plaintiff's alleged loss of between 50 and 70 percent of its market was insufficient to allege irreparable harm) (citing *Mead Johnson Pharm. Grp. v. Bowen*, 655 F. Supp. 53 (D.D.C. 1986) (holding that alleged loss of 20-to-30 percent of market share is inadequate to establish irreparable harm)); *see also ViroPharma, Inc. v. Hamburg*, 898 F. Supp. 2d 1, 26-27 (D.D.C. 2012).

Prometheus's only other claim—that RLI's "entry on the market with a separate REMS will cause irreparable reputational harm to Prometheus [due to t]he frustration, ill will, and increased costs experienced by prescribers, pharmacists, and patients in complying with two separate REMS," Prometheus Br. at 20—is mystifying. Given that patients and the prescribers and pharmacists who treat them have for years been clamoring for a generic alternative to Prometheus's pricey Lotronex® product, it is hard to imagine that FDA's decision will meet with anything other than relief that a generic alternative is finally available—and even less plausible to think that patients, prescribers, and pharmacists will blame Prometheus for anything other than its anticompetitive scheme to prevent the

availability of a safe, effective, and affordable generic substitute. But even if it were true that Prometheus somehow stands to lose long-term relationships from generic market entry in these circumstances, *id.* at 20, that will result not from Prometheus's customers' *frustration* that generic products finally are available, but from their *preference* to purchase products from RLI—a choice that Congress of course hoped would follow from the ordinary and intended operation of the Hatch-Waxman Act.

B. The Balance Of Hardships Weighs Heavily Against Prometheus.

Nor has Prometheus shown clearly that the balance of hardships weighs in its favor. Its only argument here is that RLI and FDA "will not be burdened" by the entry of a TRO "because neither has any legitimate interest in engaging in action that is contrary to the APA and the FDCA." Prometheus Br. at 22. But that simply begs the question of whether Prometheus is right on the merits—which, for the reasons set forth above, it is not.

Nor is it true that Prometheus's requested TRO would preserve the status quo. RLI has a legal right to market its product in interstate commerce pursuant to a lawful approval whose effectiveness Prometheus seeks to suspend. *But see Elk Assocs. Funding Corp. v. U.S. Small Bus. Admin.*, 858 F. Supp. 2d 1, 31 n.28 (D.D.C. 2012) (noting that granting "mandatory relief altering the status quo … is generally disfavored") (citing *Allina Health Servs. v. Sebelius*, 756 F. Supp. 2d 61, 69-70 (D.D.C. 2010)). RLI has spent years diligently pursuing FDA approval in order to secure that right, and the entry of a TRO would cause RLI to suffer literally

millions of dollars in planning costs and lost sales that the Company can never recoup. *See* Peterman Decl. ¶¶ 12-15, 18-20.

Moreover, and in contrast to Prometheus's mystifying claim that its reputation and customer goodwill will suffer, the entry of a TRO actually will disrupt RLI's reputation and goodwill with its customers. In full reliance on FDA's lawful approval, RLI has sent approximately 24,500 letters informing retail pharmacists that its product will be available imminently pursuant to FDA's approval, and it has negotiated contracts with dozens of its customers, who are expecting to receive RLI's product imminently. *See id.* at ¶¶ 12-16, 19. RLI also has redirected considerable physical and human resources to its planned launch. Prometheus's last-minute filing, two full weeks after FDA announced its approval and calculated to cause maximum disruption to these commercial plans, now threatens to disrupt all of these efforts and undermine the company's commercial relationships in a manner the courts repeatedly have found sufficient to tilt the balance of hardships against injunctive relief. *See, e.g.*, *Sandoz*, 439 F. Supp. 2d at 32-33 (declining to enter injunctive relief against an imminent generic launch because "entry of an order barring intervenor-defendants from marketing their generic simvastatin product would preclude them from fulfilling the contracts they have negotiated with major simvastatin purchasers, … [which] would not only undercut intervenor-defendants' ability to negotiate additional long-term contracts, but could also potentially harm intervenor-defendants by destroying goodwill and impairing their future access to major customers").

C. The Public Interest Weighs Heavily Against Injunctive Relief.

Finally, the public stands to lose the most from entry of a TRO. The whole point of the Hatch-Waxman Act is to "'get generic drugs into the hands of patients at reasonable prices—fast.'" *Andrx Pharm., Inc. v. Biovail Corp. Int'l*, 256 F.3d 799, 809 (D.C. Cir. 2001) (quoting *In re Barr Labs., Inc.*, 930 F.2d 72, 76 (D.C. Cir. 1991)). Yet suspending the effectiveness of RLI's FDA approval would deprive patients of the substantial savings they stand to secure from RLI's planned product launch by forcing them to continue purchasing Lotronex® at monopoly prices—and, in direct contravention of Congress's intent, would reward Prometheus's unlawful effort to use its ETASUs as a means to forestall generic competition and deprive patients who depend on this treatment of access to a safe, effective, and affordable generic alternative. *See* 21 U.S.C. § 355-1(f)(8).

Once again, Prometheus's only answer is that the public has an "interest in seeing that laws are faithfully executed by public officials." Prometheus Br. at 19 (citations omitted). But that truism simply begs the question of who is right on the merits. And while Prometheus briefly asserts that the public interest weighs in favor of injunctive relief because RLI's waiver "will result in patients and providers being forced to navigate two separate REMS for alosetron hydrochloride," *id.* at 18-19, that too is the natural and intended outcome of the statute—which expressly allows generic applicants to use "a different, comparable aspect of the elements to assure safe use" where FDA exercises its congressionally-delegated authority to make this quintessential policy determination. If Prometheus thinks that waivers do not serve the public interest, its remedy lies with Congress, not this Court.

CONCLUSION

For the foregoing reasons, the motion should be denied.

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Respectfully submitted,

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CERTIFICATE OF SERVICE

The undersigned certifies that on this 20th day of May, 2015, he caused a copy of the foregoing MEMORANDUM OF POINTS AND AUTHORITIES IN OPPOSITION TO MOTION FOR TEMPORARY RESTRAINING ORDER to be served upon the following attorneys via the Court's ECF filing system and electronic mail:

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