IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

UNITED THERAPEUTICS CORPORATION,
1040 Spring Street
Silver Spring, MD 20910

Plaintiff,

v.

UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES,
200 Independence Avenue, S.W.
Washington, DC 20201;

THOMAS E. PRICE, M.D.,
in his official capacity as SECRETARY,
UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES,
200 Independence Avenue, S.W.
Washington, D.C. 20201;

UNITED STATES FOOD AND DRUG ADMINISTRATION,
10903 New Hampshire Avenue
Silver Spring, MD 20993;

and

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

Defendants.

Civil Action No. _____

COMPLAINT FOR DECLARATORY AND INJUNCTIVE RELIEF

Plaintiff United Therapeutics Corporation ("UTC") brings this complaint for declaratory and injunctive relief, and states the following in support thereof:

PRELIMINARY STATEMENT

1. This is an action to require the U.S. Food and Drug Administration ("FDA" or the "Agency") to follow the plain language of the Orphan Drug Act and grant UTC the statutory exclusivity required by law. Congress, in the Orphan Drug Act, provided statutory incentives to pharmaceutical companies developing "orphan drugs," *i.e.*, drugs that treat rare conditions and diseases that would ordinarily be unprofitable due to the limited market for those drugs. *See* Orphan Drug Act, Pub. L. No. 97-414, § 1(b)(4), 96 Stat. 2049, 2049 (1983) (making statutory findings); *see also* H.R. Rep. No. 97-840, at 1 (1982). The most important of these incentives is a seven-year period of market exclusivity, known as "orphan drug exclusivity."

2. Under the Orphan Drug Act, a pharmaceutical company may request that FDA designate its drug as an "orphan drug." 21 U.S.C. § 360bb. To receive such a designation, the pharmaceutical company must show that its drug is being investigated for a rare disease or condition and, if approved, would be approved for use in that disease or condition. *Id.* § 360bb(a). If a previously designated orphan drug ultimately receives FDA approval, finding that the drug is safe and effective for the designated orphan disease or condition, then by statute the drug is automatically entitled to a seven-year period of exclusivity. *Id.* §§ 360cc(a), 355.

3. FDA designated Plaintiff's drug treprostinil as an orphan drug for the treatment of pulmonary arterial hypertension (PAH). On December 20, 2013, Plaintiff obtained FDA approval for Orenitram® (treprostinil) Extended-Release Tablets, an oral version of treprostinil in

an extended-release tablet dosage form in various strengths, for the treatment of PAH, and thus was automatically entitled to exclusivity for seven years from the date of approval. Nevertheless, FDA has unlawfully denied Orenitram its statutorily mandated exclusivity. FDA claimed that in order to receive orphan drug exclusivity for the oral formulation of treprostinil for use in the treatment of PAH, UTC "must demonstrate that oral treprostinil is clinically superior to the other treprostinil formulations by means of greater efficacy, greater safety or a major contribution to patient care (MCTPC)." Letter from Gayatri R. Rao, Director, FDA Office of Orphan Products Development, to Frank J. Sasinowski, Hyman, Phelps & McNamara, P.C., at 2 (Mar. 23, 2016) [hereinafter 2016 Letter]. FDA's unlawful application of this "clinical superiority" standard to obtain orphan drug exclusivity is the subject of this litigation.

4. This is not the first time that FDA's refusal to follow the plain language of the Orphan Drug Act has required court intervention. In 2014, Judge Ketanji Brown Jackson held, in almost identical circumstances, that the "plain language of the exclusivity provision of the Orphan Drug Act requires the FDA to recognize exclusivity for any drug that the FDA has designated and granted marketing approval . . . ." *Depomed, Inc. v. U.S. Dep't of Health & Human Servs.*, 66 F. Supp. 3d 217, 237 (D.D.C. 2014). Judge Jackson held unlawful FDA's requirement that a drug that had been granted orphan drug designation needed to prove clinical superiority to older, similar drugs to be entitled to exclusivity. Judge Jackson recognized that FDA's extra-statutory limits on exclusivity were fundamentally in conflict with the statute. *See id.* at 229. FDA did not appeal the *Depomed* ruling, and published a notice explaining its intent to treat that decision as limited to its facts and to "continue to apply its existing regulations." Policy on Orphan-Drug Exclusivity; Clarification, 79 Fed. Reg. 76,888 (Dec. 23, 2014). There is

no basis, however, for FDA's refusal to follow *Depomed*. Judge Jackson's ruling was based on the plain language of an unambiguous statute. It in no way depended on the facts of the case.

5. There is another case pending before this Court involving these same issues: *Eagle Pharmaceuticals, Inc. v. Burwell*, No. 1:16-cv-00790 (D.D.C. filed Apr. 27, 2016) (J. Kessler). Cross-motions for summary judgment were filed earlier this year in which FDA continues to take the position that the *Depomed* ruling does not deserve deference.

6. Based on its intransigence, there is no doubt that FDA disagrees with the policy behind Congress's structure of the Orphan Drug Act. But FDA is not free to simply disregard the plain language of the statute and *Depomed*. Had FDA respected Judge Jackson's ruling in 2014, the *Eagle Pharmaceuticals* case and this case would not be necessary.

7. Unless enjoined by this Court, Defendants' conduct will undermine the congressionally enacted incentives for companies to develop orphan products and will cause significant economic harm to Plaintiff. Plaintiff is aware of at least one application pending at FDA seeking approval to market a generic version of treprostinil to treat PAH that would directly compete with Orenitram. If FDA had appropriately granted orphan drug exclusivity to Orenitram, FDA could not approve other drugs before December 20, 2020. UTC seeks declaratory and injunctive relief to overturn Defendants' illegal acts and to obtain for Orenitram the orphan drug exclusivity to which it is entitled.

PARTIES

8. UTC is a corporation organized and existing under the laws of the State of Delaware, having a place of business at 1040 Spring Street, Silver Spring, Maryland 20910. UTC is a biotechnology company focused on the development and commercialization of products designed to address the needs of patients with chronic and life-threatening conditions.

9. Defendant U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES is an executive department of the United States with its headquarters and principal place of business at 200 Independence Avenue, SW, Washington, D.C. 20201.

10. Defendant THOMAS PRICE is the Secretary of Health and Human Services and is ultimately responsible for the implementation and execution of the Federal Food, Drug, and Cosmetic Act ("FDC Act"), the Orphan Drug Act, and associated regulations. The Secretary exercises those authorities through FDA, an agency within the U.S. Department of Health and Human Services.

11. Defendant FDA is a federal agency within Defendant U.S. Department of Health and Human Services. FDA has responsibility, *inter alia,* for approving and regulating drugs sold within the United States, including through application of the Orphan Drug Act. The headquarters and principal place of business of FDA is 10903 New Hampshire Avenue, Silver Spring, Maryland 20903.

12. Defendant SCOTT GOTTLIEB is the Commissioner of FDA and is directly responsible for FDA's implementation and execution of the FDC Act, the Orphan Drug Act, and associated regulations. In that role, Dr. Gottlieb heads FDA and reports to Defendant Price.

JURISDICTION AND VENUE

13. This Court has subject matter jurisdiction over Plaintiff's claims pursuant to 28 U.S.C. §§ 1331, 1346, and 1361, as well as 5 U.S.C. §§ 702, 706. This Court has authority to grant declaratory relief pursuant to 28 U.S.C. §§ 2201 and 2202.

14. This Court has personal jurisdiction over Defendants, as each is an agency or official of the United States Government.

15. Venue is proper in this Court pursuant to 28 U.S.C. § 1391(b) and (e).

LEGAL AND REGULATORY FRAMEWORK

A. The Orphan Drug Act

16. The Orphan Drug Act was enacted on January 4, 1983, to incentivize the development of drugs for rare diseases and conditions. Pub. L. No 97-414, § 1(b), 96 Stat. at 2049; *see also* H.R. Rep No. 97-840, at 1. The Orphan Drug Act amended the FDC Act at 21 U.S.C. §§ 360aa-360ee. By enacting the Orphan Drug Act, Congress provided financial incentives to encourage investment in the development of drugs that would otherwise not be developed because the market for their use was too small to be profitable.

17. The main financial incentive established by Congress through the Orphan Drug Act is a seven-year period of marketing exclusivity for approved orphan drugs. During this period of exclusivity, FDA may not approve another marketing application for "such drug" for "such disease or condition." 21 U.S.C. § 360cc(a). No new entity is permitted to manufacture or sell the drug in interstate commerce for the orphan indication during that time. Congress's decision to grant orphan drug holders seven years of marketing exclusivity upon approval was the result of purposeful consideration of the extent of benefits needed to incentivize drug manufacturers to advance treatments for orphan diseases. *See* H.R. Rep. No. 100-473, at 6 (1987) (describing how Congress considered the potential benefits and drawbacks of offering seven years of market exclusivity).

18. The plain language of the statute sets forth two procedural prerequisites for marketing exclusivity: first, FDA must have "designated" the drug as an orphan drug pursuant to 21 U.S.C. § 360bb, and second, FDA must have "approved" the designated orphan drug for marketing to the public.

19. Section 526 of the FDC Act (21 U.S.C. § 360bb) establishes the process by which a drug may receive orphan designation. That section requires FDA to grant a timely request for an orphan drug designation if the Agency finds that: (a) the drug is being investigated for a rare disease or condition; and (b) if the drug is approved, the approval will be for the use of the drug for that rare disease or condition.

20. Once a drug is designated as an orphan drug and is approved as safe and effective for the designated use, it is entitled to market exclusivity:

> Except as provided in subsection (b), if [FDA] – (1) approves an application filed pursuant to [21 U.S.C. § 355] . . . for a drug designated under [21 U.S.C. § 360bb] for a rare disease or condition, [FDA] may not approve another application . . . for such drug for such disease or condition for a person who is not the holder of such approved application . . . until the expiration of seven years from the date of the approval of the approved application . . . .

21 U.S.C. § 360cc(a).

B. FDA Regulations Implementing the Orphan Drug Act

21. Congress permitted FDA to promulgate regulations implementing the designation provision of the Orphan Drug Act. *Id.* § 360bb(d). FDA regulations provide that FDA will grant a timely submitted request for orphan drug designation if the drug is intended for a rare disease or condition, and there is sufficient information to establish that a medically plausible basis exists to expect the drug to be effective in the prevention, diagnosis, or treatment of that disease or condition. *See* 21 C.F.R. §§ 316.24(b), 316.25.

22. The regulations further provide that FDA can refuse to grant an orphan drug designation if "[t]he drug is otherwise the same drug as an already approved drug for the same rare disease or condition and the sponsor has not submitted a medically plausible hypothesis for the possible clinical superiority of the subsequent drug." *Id.* § 316.25(a)(3). The regulations

define "same drug," in relevant part, as "a drug that contains the same active moiety as a previously approved drug and is intended for the same use as the previously approved drug." *Id.* § 316.3(b)(14)(i). An FDA regulation defines the term "active moiety" to mean "the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance." *Id.* § 316.3(b)(2).

23. Although Congress did not direct FDA to promulgate regulations implementing the exclusivity provision in the Orphan Drug Act, *see* 21 U.S.C. § 360cc; *see also Depomed,* 66 F. Supp. 3d at 222 (noting that FDA was not delegated authority to promulgate implementing regulations for the Orphan Drug Act's exclusivity provision), FDA did so nonetheless.

24. FDA's orphan drug exclusivity regulations are different from the statutory design of FDC Act § 527 (21 U.S.C. § 360cc) in one material way. Namely, FDA's regulations permit FDA to withhold exclusivity for an orphan-designated drug if there is an already-approved orphan drug that is the same drug for the same orphan disease or condition, unless the sponsor can *prove* that its drug is in fact "clinically superior" to the previously approved drug. *See* 21 C.F.R. §§ 316.31(a), 316.34(c). In other words, FDA has given itself authority found nowhere in the statute to withhold the statutory orphan drug exclusivity Congress utilized to incentivize the development of these drugs. Nothing in the Orphan Drug Act permits FDA to approve a drug with an orphan designation and withhold orphan drug exclusivity.

25. FDA continues to apply this extra-statutory requirement for proof of clinical superiority despite the fact that the same requirement was expressly rejected by Judge Jackson in

Depomed. With no explanation, FDA claimed that the *Depomed* decision was limited to the facts of that case:

> It is the Agency's position that, given the limited terms of the court's decision to GRALISE, FDA intends to continue to apply its existing regulations in part 316 to orphan-drug exclusivity matters. FDA interprets section 527 of the [FDC Act] and its regulations (both the older regulations that still apply to original requests for designation made on or before August 12, 2013, as well as the current regulations) to require the sponsor of a designated drug that is the 'same' as a previously approved drug to demonstrate that its drug is 'clinically superior' to that drug upon approval in order for the subsequently approved drug to be eligible for orphan-drug exclusivity.

79 Fed. Reg. at 76,888. FDA has acted and continues to act in direct conflict with both the Orphan Drug Act and Judge Jackson's holding in *Depomed.*

STATEMENT OF FACTS

A. Orenitram

26. UTC is the developer of the drug product Orenitram® (treprostinil) Extended-Release Tablets, for oral use. FDA approved Orenitram on December 20, 2013, for the treatment of PAH to improve exercise capacity. PAH is a progressive disease that is characterized by remodeling of the small to medium pulmonary arteries, leading to restricted blood flow. Restricted blood flow through the pulmonary arteries results in increased vascular resistance and, ultimately, right heart failure. Orenitram is available in five distinct strengths (0.125 mg, 0.25 mg, 1 mg, and 2.5 mg, and 5 mg), which allows physicians to prescribe specific doses depending on the needs of each individual patient.

27. Orenitram has the same active ingredient as two other FDA-approved drug products: Remodulin® (treprostinil) Injection and Tyvaso® (treprostinil) Inhalation Solution. Both of these drugs are owned and marketed by UTC. FDA approved Remodulin for

subcutaneous use on May 21, 2002, and for intravenous use on November 24, 2004. FDA approved Tyvaso for oral inhalation on July 30, 2009.

28. Although Orenitram is required to be taken with food, a solid oral extended-release dosage form of treprostinil offers PAH patients the opportunity to take their medication without the need for injections or cumbersome inhalation devices. Because treprostinil dosing is highly patient-specific and changes over time with each patient, the multiple available tablet strengths are designed to give patients the ability to use an oral treprostinil over a broad range of required doses.

29. To support the approval of Orenitram, UTC conducted three Phase 3 clinical studies in addition to the clinical studies that UTC had already conducted to support approval of the other two forms of treprostinil.

B. FDA Granted Orphan Drug Designation for Orenitram

30. The history of orphan drug designation for treprostinil for use in the treatment of PAH is circuitous, but there is no dispute that FDA has designated Orenitram an orphan drug for the treatment of PAH.

31. On June 4, 1997, FDA granted orphan drug designation for the active moiety treprostinil for use in the treatment of primary pulmonary hypertension, which was amended in November 1999 to include PAH. FDA specifically granted orphan drug designation for Tyvaso® (treprostinil) Inhalation Solution on June 17, 2010, after the approval of a marketing application for the drug product, and retroactively granted orphan drug exclusivity to Tyvaso, which exclusivity expired on July 30, 2016.

32. UTC submitted a request for orphan drug designation for Orenitram for the treatment of PAH on December 14, 2011 (Designation request #11-3621). In March 2012, FDA

denied the orphan drug designation request on two separate grounds: (1) UTC had not provided an adequate prevalence calculation; and (2) UTC had not provided an adequate hypothesis that oral treprostinil is clinically superior by a claim of a major contribution to patient care ("MCTPC") over the other inhaled form of treprostinil (*i.e.*, Tyvaso). FDA approved Orenitram on December 20, 2013, but withheld exclusivity due to its determination that the product lacked orphan drug designation.

33. Even after approval, UTC continued to seek orphan drug designation so that it could benefit from the exclusivity period. UTC submitted a response to FDA's March 2012 letter providing the requested information regarding the prevalence of PAH and why Orenitram provides a major contribution to patient care over the existing intravenous (*i.e.*, Remodulin) and inhalation (*i.e.*, Tyvaso) dosage forms of treprostinil. On March 23, 2016, FDA conceded that the product did in fact have orphan drug designation. ("Since this sponsor ***already held an orphan drug designation*** for treprostinil for use in the treatment of PAH when they filed this present application for a different treprostinil formulation for the same use in 2011, the present designation application did not need to be submitted.") (emphasis added); *id.* at 1 ("Since the sponsor ***already held orphan drug designation*** for treprostinil for use in the treatment of PAH when they filed this present orphan drug designation application for another formulation of treprostinil for the same use in 2011, as already noted above, the present designation application did not need to be submitted . . . .") (emphasis added); *id.* at 1-2. Thus, FDA confessed that UTC did not need to have requested a separate orphan drug designation for Orenitram in 2011 – because the Agency had previously designated treprostinil for the treatment of PAH. Thus, UTC did not need to provide additional information to support that designation as FDA requested in 2012.

C. FDA Withheld Orphan Drug Exclusivity

34. Because FDA admitted that Orenitram was properly designated as an orphan drug for the treatment of PAH, the statute dictated that FDA grant Orenitram market exclusivity for seven years from the date of approval. Instead, FDA denied exclusivity by applying its unlawful, extra-statutorial requirement of clinical superiority. In its March 23, 2016 letter, FDA claimed:

> [I]n order to receive orphan drug exclusivity for the oral formulation of treprostinil for use in the treatment of PAH upon marketing approval, the sponsor must demonstrate that oral treprostinil is clinically superior to the other treprostinil formulation by means of greater efficacy, greater safety or a major contribution to patient care (MCTPC).

See 2016 Letter, at 1. Despite robust information to support clinical superiority, FDA disagreed and concluded that exclusivity was not available: "Since you do not demonstrate clinical superiority of oral treprostinil over inhaled treprostinil by means of greater efficacy, greater safety or a MCTPC, you cannot receive orphan drug exclusivity for the oral treprostinil formulation for use in the treatment of PAH." *See id.* at 3. Of course, such information was not necessary in the first place, because the statute does not require a demonstration of clinical superiority to be awarded orphan drug exclusivity.

CLAIM FOR RELIEF

CLAIM 1

(Violation of the Administrative Procedure Act)

35. UTC reasserts and incorporates by reference all of the above allegations.

36. The Administrative Procedure Act prohibits Defendants from acting in a way that is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with the law, or that is in excess of statutory jurisdiction or authority or short of statutory right. 5 U.S.C. § 706(2)(A), (C).

37. Notwithstanding that the plain language of the Orphan Drug Act and the court's decision in *Depomed* require Defendants to grant orphan drug exclusivity upon approval of a previously designated orphan drug, Defendants have impermissibly denied Orenitram orphan drug exclusivity and required that UTC demonstrate that Orenitram is clinically superior to Remodulin and Tyvaso. Defendants' denial of orphan drug exclusivity for Orenitram upon approval of the drug for its orphan-designated indication was arbitrary and capricious, an abuse of discretion, exceeds Defendants' statutory authority, and is otherwise not in accordance with the law.

38. Defendants' approval of Orenitram for the treatment of PAH and their subsequent denial of the orphan drug exclusivity that such approval automatically triggered, constitutes final agency action. 5 U.S.C. § 704.

39. UTC has exhausted its administrative remedies, or, to the extent that it has not, is not required to exhaust its administrative remedies because doing so would not further the goals that exhaustion is designed to further.

40. UTC has no adequate remedy at law. *Id.* § 704.

PRAYER FOR RELIEF

WHEREFORE, UTC respectfully requests that this Court enter judgment in its favor and prays for the following relief:

A. A declaration pursuant to 28 U.S.C. § 2201 that:

   a. Defendants' refusal to grant orphan drug exclusivity to UTC for Orenitram exceeds their statutory authority, and is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with the law;

   b. UTC is entitled to seven years of orphan drug exclusivity for Orenitram for

the treatment of PAH starting from December 20, 2013, the date Defendants approved Orenitram for this indication; and

c. FDA's regulations at 21 C.F.R. §§ 316.3(b)(12), 316.31(a), 316.34(a), (c) are invalid under the FDC Act, as amended by the Orphan Drug Act, insofar as they purport to permit Defendants to not recognize orphan drug exclusivity for Orenitram.

B. An order directing Defendants to recognize that UTC is entitled to all benefits of orphan drug exclusivity approval, including publication of that status in FDA's *Approved Drug Products with Therapeutic Evaluations* ("the Orange Book") and other Agency public databases, as well as issuance of written notice, in accordance with 21 C.F.R. § 316.34(a), (b).

C. Injunctive relief effectuating UTC's orphan drug exclusivity by enjoining Defendants from approving any other drug covered by UTC's exclusivity for the treatment of PAH until December 20, 2020.

D. An order awarding UTC its costs and attorneys' fees pursuant to 28 U.S.C. § 2412; and

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

Dated: August 4, 2017

Respectfully submitted,

/s/ Anne K. Walsh
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