IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

UNITED THERAPEUTICS CORP.,	)	
Plaintiff,	)	Civil Action No. 1:17-cv-01577
v.	)	Judge Ellen S. Huvelle
UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES *et al.*,	)	
Defendants.	)	

DEFENDANTS' RESPONSE TO PLAINTIFF'S
MOTION FOR SUMMARY JUDGMENT AND CROSS-MOTION

Pursuant to the Court's order dated December 13, 2017, and Rule 7(h) of this Court's Local Rules, defendants, the United States Department of Health and Human Services, Eric D. Hargan, in his official capacity as Acting Secretary,[1] the United States Food and Drug Administration (FDA), and Scott Gottlieb, M.D., in his official capacity as Commissioner of Food and Drugs (collectively, the United States), respectfully request that the Court deny the motion for summary judgment filed by plaintiff, United Therapeutics Corporation, sustain the FDA decision at issue, and enter summary judgment in favor of the United States.

In support of this motion, we rely on the administrative record submitted in this matter and the following brief.

[1] Pursuant to Rule 25(d) of the Federal Rules of Civil Procedure, Acting Secretary Eric D. Hargan is substituted for former Secretary Thomas E. Price, M.D.

Respectfully submitted,

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December 22, 2017

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v.	)	Judge Ellen S. Huvelle
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MEMORANDUM OF LAW IN SUPPORT OF DEFENDANTS' RESPONSE TO PLAINTIFF'S MOTION FOR SUMMARY JUDGMENT AND CROSS-MOTION

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INTRODUCTION

United Therapeutics Corporation (UTC) asks the Court to grant seven years of market exclusivity for Orenitram (oral treprostinil)—a drug UTC developed to treat a rare disease called pulmonary arterial hypertension. What UTC fails to mention is that Orenitram is merely the latest in a line of such drugs. Prior to Orenitram, UTC developed two other drugs for the same purpose, using the same active ingredient (treprostinil). Each of those drugs received its *own* seven years of exclusivity. The first drug, Remodulin (intravenous and subcutaneous treprostinil) received exclusivity because it was the first drug of its kind; the second, Tyvaso (inhaled treprostinil), because it was shown to be clinically superior to the first. Orenitram is not the first, nor is it clinically superior. Yet UTC nevertheless claims that developing the drug entitles it to extend its fourteen-year monopoly on treprostinil drugs to twenty-one years. This desire for monopoly is understandable: UTC stands to reap tremendous profits if it can continue to exclude potential competitors from the market. But, contrary to what UTC argues, such a monopoly is *not* compelled by the Orphan Drug Act—and not justified given the facts of this case.

The Orphan Drug Act, 21 U.S.C. §§ 360aa *et seq.*, provides for seven years of exclusivity to drugs that the Food and Drug Administration (FDA) has designated and approved for the treatment of rare diseases or conditions. However, the statute does not specify what happens after the expiration of a drug's exclusivity—nor does it indicate whether that exclusivity can be renewed simply by re-formulating an existing drug. There are good reasons to believe that exclusivity should *not* be renewable. In enacting the Orphan Drug Act, Congress sought to incentivize meaningful advances in drug development for previously untreated rare diseases by awarding these developments with, among other things, a seven-year exclusivity period.

Congress never intended to reward companies with serial (and potentially indefinite) periods of exclusivity for minor variations to an already approved drug.

Consistent with the statute's purpose, FDA has, for more than twenty-five years, interpreted the Orphan Drug Act to confer a seven-year period of exclusivity to only the *first* drug approved as an orphan drug (meaning a drug with a new active ingredient or that is clinically superior). This interpretation is both reasonable and deserving of deference. Indeed, Congress recently affirmed this interpretation in enacting the FDA Reauthorization Act of 2017.[1] Under this interpretation, UTC is not entitled to continue its monopoly, because Orenitram is neither novel nor clinically superior to the previously-approved versions of treprostinil. Orenitram should be denied exclusivity, as FDA correctly decided. An alternative result would be anathema to the Orphan Drug Act's underlying purpose, and would create a windfall for UTC to the detriment of patients with a rare disease.

Accordingly, we respectfully request that the Court sustain FDA's decision, and enter judgment in favor of the United States.

BACKGROUND

I. STATUTORY AND REGULATORY FRAMEWORK

A. Drug Approval Process

Under the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. §§ 301 *et seq.*, pharmaceutical companies seeking to market an initial version of a drug must first obtain FDA approval by filing a new drug application (NDA) containing extensive scientific clinical data demonstrating the safety and effectiveness of the drug. *See* 21 U.S.C. § 355(a), (b), (c).

[1] Congress recently enacted the FDA Reauthorization Act of 2017, Pub. L. No. 11-52, 131 Stat. 1005, which, among other things, amends the exclusivity provision of the Orphan Drug Act, 21 U.S.C. § 360cc. Unless otherwise noted, references to 21 U.S.C. § 360cc are to the statute at the time UTC sought orphan drug exclusivity for Orenitram.

Sponsors of NDAs may be able to delay approval of other applications for the same drug by obtaining and listing patents and qualifying for statutory bars on FDA approval (*i.e.*, exclusivities).

The Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments) amended the Act to add, among other provisions, 21 U.S.C. § 355(b)(2) and 21 U.S.C. § 355(j), which provide abbreviated pathways for new drug approval. The Hatch-Waxman Amendments reflect Congress's efforts to balance the need to "make available more low cost generic drugs by establishing a generic drug approval procedure" with new incentives for drug development in the form of exclusivity and patent term extensions. *See* H.R. Rep. 98-857, at 14 (June 21, 1984) [FDA 1716].[2] FDA approves drug applications submitted pursuant to 21 U.S.C. § 355(b)(2) and 355(j), when they have met all requirements for approval and any applicable patent and exclusivity periods have expired or have otherwise ceased to be a barrier.

B. Orphan Drug Act and Related Regulations

In 1983, one year before the passage of the Hatch-Waxman Amendments, Congress enacted the Orphan Drug Act to provide incentives to develop "orphan drugs" for the treatment of "rare diseases and conditions." *See* H.R. Rep. 97-840, Pt. 1, at 5 (Sept. 17, 1982) [FDA 1695].[3] These incentives include tax credits for clinical testing, exemption from application user fees, and the possibility of seven years of orphan drug exclusivity. *See* H.R. Rep. 97-840, Pt. 1, at 5 [FDA 1695]; 21 U.S.C. §§ 360ee, 379h(a)(1)(F); 26 U.S.C. § 45C. Without these incentives, rare diseases and conditions "affect such a small number of persons that there is

[2] "[FDA __]" refers to the corresponding page in the administrative record filed in this case.

[3] Congress explained that drugs for rare diseases or conditions are "commonly referred to as 'orphan drugs'" because "[t]hey generally lack a sponsor to undertake the necessary research and development activities to attain their approval by the [FDA]." H.R. Rep. 97-840, Pt. 1, at 6 [FDA 1696].

virtually no commercial value to any drug which is useful against them," and sponsors have no incentive to support research and drug approval in these circumstances. H.R. Rep. 97-840, Pt. 1, at 6 [FDA 1696]; *see also* 21 U.S.C. § 360bb(a)(2) (defining "rare disease or condition" as a disease or condition affecting fewer than 200,000 in the United States).

1. Orphan Drug Designation

To obtain many of these incentives, sponsors of drugs for rare diseases must first seek and obtain "designation" for their drugs under 21 U.S.C. § 360bb. *See also* 21 C.F.R. §§ 316.31, 316.34 (2011).[4] The sponsor must submit to FDA a request for designation that includes, among other things, a "description of the rare disease or condition for which the drug is being or will be investigated, the proposed use of the drug, and the reasons why such therapy is needed." 21 C.F.R. § 316.20(b)(3); *see generally* 21 C.F.R. §§ 316.20, 316.21.

If a drug is the same as "an already approved drug" for the same use (*i.e.*, the drugs contain the same active moiety),[5] the sponsor must include in the designation request "a plausible hypothesis that its drug may be clinically superior to the first drug." 21 C.F.R. § 316.20(a), (b)(5). Under this framework, a sponsor is able to secure the benefits of designation—such as tax credits for clinical testing, which help defray the costs of development at an early stage of the process—by presenting a *plausible hypothesis* of clinical superiority, but without having to *demonstrate* clinical superiority before testing is complete.

[4] Because this version of the regulations was in effect when UTC first requested designation, it is the one applicable to this case. Unless otherwise noted, references to the Code of Federal Regulations are to this version of the regulation.

[5] The term "active moiety," as defined in 21 C.F.R. § 316.3(b)(2), means the portion of the drug that is likely responsible for the activity of the molecule, and ignores certain parts of the molecule that generally result in clinically insignificant changes to its chemical structure (such as salt and ester bonds). It is undisputed that the drugs at issue here contain the same active moiety (*i.e.*, treprostinil).

2. Orphan Drug Exclusivity

One of the major incentives in the Orphan Drug Act, and the provision at issue here, is orphan drug exclusivity. Before Congress's recent amendment to the exclusivity provision of the Orphan Drug Act, the statute stated in relevant part:

> **Protection for drugs for rare diseases or conditions**
>
> (a) Exclusive approval, certification, or license
> Except as provided in subsection (b), if the Secretary—
>
> (1) approves an application filed pursuant to section 355 of this title, or
>
> (2) issues a license under section 262 of title 42
>
> for a drug designated under section 360bb of this title for a rare disease or condition, the Secretary may not approve another application under section 355 of this title or issue another license under section 262 of title 42 *for such drug* for such disease or condition for a person who is not the holder of such approved application or of such license until the *expiration* of seven years from the date of the approval of the approved application or the issuance of the license.

21 U.S.C. § 360cc(a) (emphasis added). Under this provision, FDA will generally recognize seven years of exclusivity for drugs with orphan designations upon approval of those drugs for those indications within the designated disease or condition. *Id.* During this exclusivity period, FDA will not approve any other application for the same drug for the same indication.

The statute does not specify whether there may be multiple exclusivity periods for a particular drug. Rather, Congress refers only to an approved drug and subsequent "such drug" without further definition. 21 U.S.C. § 360cc; *see also* Orphan Drug Regulations, 57 Fed. Reg. 62,076, 62,078 (Dec. 29, 1992) (noting that Congress left it to FDA to define "such drug") [FDA 1793]; *Baker Norton Pharm., Inc. v. U.S. Food & Drug Admin.*, 132 F. Supp. 2d 30, 36 (D.D.C. 2001) ("Given the multiple definitions of the term 'drug,' and the differing purposes that various

statutory provisions can serve, the Court cannot find that the definition of 'drug' in § 360cc(a) is clear and unambiguous."). Nor does the statute describe the implications of the "expiration" of an orphan drug's exclusivity. The issue, then, is how the terms "such drug" and "expiration" should be interpreted to effect the statute's purpose.

After extensive consideration of the Orphan Drug Act's text and purpose, FDA issued a final rule in 1992 to implement its interpretation of the designation and exclusivity provisions of the Orphan Drug Act.[6] *See generally* 57 Fed. Reg. 62,076 [FDA 1791]. Among other things, the 1992 regulations describe the rules that apply when a sponsor of a subsequent version of a drug seeks designation and exclusivity for the same indication as a previously approved drug. While the sponsor at the designation stage need only present a plausible hypothesis of clinical superiority, it needs to *demonstrate* such superiority at the approval stage to qualify for seven-year orphan drug exclusivity.[7]

Specifically, under this "clinical superiority" framework, if a sponsor seeks to market a new version of an already approved drug for the same use (even one sharing the same chemical structure), it must demonstrate that the new version is clinically superior to the previously approved drug to avoid being the same "such drug" and potentially blocked by the already approved drug's exclusivity period. *See* 21 C.F.R. § 316.3(b)(13) (defining "same drug" and excluding a "clinically superior" drug from that definition). This regulatory framework ensures that there will not be serial, potentially infinite, seven-year periods of orphan drug exclusivity for

[6] The 1992 regulations, which were in effect when UTC initially sought orphan drug designation for Orenitram, apply here. FDA amended its orphan drug regulations in 2013 to further clarify its long-standing view that this framework requires sponsors of subsequent versions of a drug to demonstrate clinical superiority over a previously approved drug to obtain exclusivity. *See generally* 78 Fed. Reg. at 35,132 [FDA 1835].

[7] Demonstrating clinical superiority is a more rigorous showing than the plausible hypothesis of clinical superiority required at the designation stage. *See* 21 C.F.R. § 316.3(b)(3) ("Clinically superior means that a drug is shown to provide a significant therapeutic advantage").

the "same" drug (*i.e.*, a drug that has the same active moiety and is approved for the same indication as a previously approved drug, but has not been shown to be clinically superior).

A sponsor may demonstrate clinical superiority by showing that, as compared to the previously approved drug, its drug provides a "significant therapeutic advantage" by providing greater effectiveness or safety, or otherwise makes a "major contribution to patient care." 21 C.F.R. § 316.3(b)(3). To show greater safety or effectiveness, sponsors may need to present evidence in the form of direct comparative clinical trials. *See id.* § 316.3(b)(3)(i), (b)(3)(ii). A finding that a drug makes a major contribution to patient care is reserved for "unusual cases." *Id.* § 316.3(b)(3)(iii); *see also* Proposed Rule: Orphan Drug Regulations, 56 Fed. Reg. 3338, 3343 (Jan. 29, 1991) (characterizing major contribution to patient care as a "narrow category") [FDA 1782]. FDA expressed particular concern that this standard "is not intended to open the flood gates to FDA approval for every drug for which a minor convenience over and above that attributed to an already approved orphan drug can be demonstrated." 57 Fed. Reg. at 62,077 [FDA 1792]. The final determination of clinical superiority is made on a case-by-case basis. *See id*. at 62,079 [FDA 1794].

C. The *Depomed* Decision

In 2013, Depomed, Inc. challenged the clinical superiority framework after its drug Gralise (gabapentin) did not qualify for orphan drug exclusivity. *See Depomed, Inc. v. U.S. Dep't of Health & Human Servs.*, 66 F. Supp. 3d 217 (D.D.C. 2014). FDA previously approved Neurontin, a gabapentin drug first developed by Pfizer. *Id.* at 223. Pfizer, however, had not sought orphan drug designation or exclusivity for Neurontin. *Id.* at 223-24. FDA eventually granted an amended request for orphan drug designation for Gralise, finding that the data presented was adequate to show a plausible hypothesis of clinical superiority over Pfizer's

Neurontin. *Id.* at 225-26. However, when FDA approved Gralise, the agency determined that the sponsor had not demonstrated that Gralise was in fact clinically superior to Neurontin—meaning that it was the same drug as Neurontin and, therefore, not eligible for orphan drug exclusivity. *Id.* at 226.

Depomed argued that it was not required to demonstrate clinical superiority because exclusivity should have been automatic once FDA designated and approved Gralise. *Id.* at 220. The district court agreed, and ordered FDA to recognize exclusivity for Gralise, noting that the case did "not raise the specter of the 'serial exclusivity' scenario," because the first approved drug, Neurontin, had not itself received a period of orphan drug exclusivity. *Id.* at 237. The district court concluded that the facts in *Depomed* were *sui generis* because serial exclusivity "rarely, if ever, actually occurs." *Id.* at 236-37.

FDA complied with the district court order for *Depomed*, but subsequently published a notice in the Federal Register announcing that the agency would continue to implement its long-standing clinical superiority framework for designation and exclusivity decisions. *See* Policy on Orphan-Drug Exclusivity: Clarification, 79 Fed. Reg. 76,888 (Dec. 23, 2014) [FDA 1839].[8]

D. FDA Reauthorization Act of 2017

The version of the statute analyzed by the Court in *Depomed* remained in effect until earlier this year, when the President signed into law the FDA Reauthorization Act of 2017 (FDARA). *See* FDARA, Pub. L. No. 115-52, 131 Stat. 1005 [FDA 1840-1925]. Among other things, the FDARA amended the Orphan Drug Act, explicitly incorporating FDA's existing

[8] FDA explained that it would continue to interpret 21 U.S.C. § 360cc and regulations—both the 1992 regulations, which apply here, and those promulgated in 2013, *see supra* note 6—"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. 76,888 [FDA 1839].

approach to orphan drug exclusivity into the language of the statute. Specifically, the statute provides:

> If a sponsor of a drug that is designated under section 526 and is otherwise the same, as determined by the Secretary, as an already approved . . . drug is seeking exclusive approval . . . for the same rare disease or condition as the already approved drug, the Secretary shall require such sponsor, as a condition of such exclusive approval . . . to demonstrate that such drug is clinically superior to any already approved . . . drug that is the same drug.

Id. § 607(a)(3) [FDA 1884]. Further, the FDARA includes a "Rule of Construction," which expressly preserves FDA's pre-enactment exclusivity determinations: "Nothing in the amendments shall affect any determinations under [the exclusivity provision of the Orphan Drug Act] made prior to the date of enactment." *Id.* § 607(b) [FDA 1885].

II. STATEMENT OF FACTS

UTC developed the drug at issue in this case, Orenitram, for the treatment of pulmonary arterial hypertension (PAH). PAH is a disease characterized by restricted blood flow in the pulmonary arterial circulation, which can result in increased pulmonary vascular resistance and right heart failure.[9] Orenitram contains the active ingredient treprosintil, and delivers it in the form of an extended-release oral tablet. Orenitram is the third treprosintil drug that UTC has developed to treat PAH.

A. UTC Obtains Orphan Drug Exclusivity For Remodulin (Intravenous And Subcutaneous Treprostinil)

UTC developed the first such drug, Remodulin (intravenous and subcutaneous treprostinil), sometime before 2000. In 1999, FDA granted UTC's request to designate Remodulin as an orphan drug for the treatment of PAH. *See* Letter from Dean Bunce, United

[9] *See* Vallerie V. McLaughlin et al., *ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension*, 119 Circulation 2250, 2252-53 (2009) [FDA 643-44].

Therapeutics Corp., to Marlene Haffner, FDA (Oct. 13, 1999) [FDA 1416-1653]; Letter from Marlene E. Haffner, FDA, to Dean Bunce, United Therapeutics Corp. (Nov. 2, 1999) [FDA 1668]. Subsequently, FDA approved Remodulin for the treatment of PAH in subcutaneous and intravenous uses. *See* Letter from Robert Temple, FDA, to Dean Bunce, United Therapeutics Corp. (May 21, 2002) [FDA 1670-73]; Letter from Norman Stockbridge, FDA, to Dean Bunce, United Therapeutics Corp. (Nov. 24, 2004), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/021272 Orig1s002.pdf.

On June 5, 2002, FDA recognized seven-year orphan drug exclusivity for Remodulin as the first sponsor of treprostinil to obtain marketing approval for PAH, with the exclusivity period expiring on May 21, 2009. *See* Letter from Marlene E. Haffner, FDA, to Dean Bunce, United Therapeutics Corp. (June 5, 2002) [FDA 1687-89].

B. UTC Obtains Orphan Drug Exclusivity For Tyvaso (Inhaled Treprostinil) On The Basis Of Clinical Superiority

After Remodulin, UTC developed and sought orphan drug designation for Tyvaso, an inhaled formulation of treprostinil, for the treatment of PAH.[10] *See* Letter from Mary L. Grice,

[10] Designation is "conferred to the active moiety rather than the product formulation" and "changes to the product formulation should not generally affect orphan drug designation status." *See* FDA, *For Industry, Developing Products for Rare Diseases & Conditions, Designating an Orphan Product: Drug and Biological Products, Frequently Asked Questions (FAQ)*, https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseases Conditions/HowtoapplyforOrphanProductDesignation/ucm240819.htm (last visited Dec. 6, 2017) (hereinafter "Orphan Drug Designation FAQ"); *see also* Letter from Gayatri R. Rao, FDA, to Frank J. Sasinowski, Hyman, Phelps & McNamara, P.C., at 1–2 (Mar. 23, 2016) [FDA 443-33]. For purposes of exclusivity, however, the changed formulation will not receive a new period of exclusivity "unless the sponsor can demonstrate that the changed formulation is clinically superior to the original approved product." *See* Orphan Drug Designation FAQ. Accordingly, because FDA previously granted orphan drug designation to UTC for treprostinil in the treatment of PAH (*i.e.*, for Remodulin), UTC was not technically required to submit a request to designate Tyvaso for the treatment of PAH. In order for FDA to recognize exclusivity for Tyvaso, UTC was required to demonstrate that Tyvaso is clinically superior to Remodulin.

FDA, to Robert Roscigno, Lung Rx, Inc. (May 11, 2004) [FDA 779].[11] In the request, UTC argued that Tyvaso was clinically superior because it showed "greater safety" as compared to Remodulin by "eliminat[ing] the most common treatment-related adverse events experienced by patients [i.e., infusion site pain and reaction]." *See* FDA Review of Request for Orphan-Drug Designation: Designation Request 04-1891, at 4 [FDA 784] (internal quotations omitted). UTC also argued that the "change in treprostinil dosage forms from subcutaneous to inhalation is a type of change FDA has recognized as a viable candidate for demonstrating clinical superiority based on a major contribution to patient care." *Id.* (internal quotations omitted).

FDA concluded that UTC had not presented a plausible hypothesis of clinical superiority, because a "convincing hypothesis of greater safety cannot be meaningfully entertained until at least some clinically-relevant evidence of comparable treatment effectiveness has been established." *See* Letter from Marlene E. Haffner, FDA, to Frank Sasinowski, Hyman, Phelps & McNamara, P.C., at 2 (Sept. 22, 2004) [FDA 790]. Absent any clinical data on Tyvaso, it was unclear whether Tyvaso, as compared with Remodulin, was associated with similarly frequent and serious adverse events.

On March 16, 2009, UTC submitted an amended designation request. *See* Letter from Frank J. Sasinowski, Hyman, Phelps & McNamara, P.C., to Timothy Coté, FDA (Mar. 16, 2009) [FDA 801-967]. In anticipation of a meeting with FDA to discuss its designation request, UTC also submitted additional materials on July 20, 2009. *See* Letter from Frank J. Sasinowski, Hyman, Phelps & McNamara, P.C., to Timothy Coté, FDA (July 20, 2009) [FDA 990-1111]. On August 4, 2009, UTC submitted a second amended designation request. *See* Letter from Frank J. Sasinowski, Hyman, Phelps & McNamara, P.C., to Timothy Coté, FDA (Aug. 4, 2009)

[11] United Therapeutics Corp. was previously known as Lung Rx, Inc. *See* Letter from Dean Bunce, United Therapeutics Corp., to Marlene Haffner, FDA (Oct. 15, 1999) [FDA 1665].

[FDA 1132-1186]. In these supplemental materials, UTC included additional data on adverse events associated with Tyvaso and Remodulin.

On July 30, 2009, FDA approved Tyvaso for the treatment of PAH. *See* Letter from Norman Stockbridge, FDA, to Dean Bunce, United Therapeutics Corp. (July 30, 2009) [FDA 1112-17]. On April 6, 2010, at UTC's request, the company again met with FDA to discuss designating Tyvaso as an orphan drug. *See* Letter from Norman Stockbridge, FDA, to Dean Bunce, United Therapeutics Corp. (May 3, 2010) [FDA 1197-1201].

After meeting with the company and reviewing the additional materials submitted to support a claim of clinical superiority, FDA found that UTC had demonstrated clinical superiority of Tyvaso over Remodulin. Although both drugs were associated with different adverse events, in light of the data related to severe injection-site pain for Remodulin patients, FDA concluded that Tyvaso "offered a valuable alternative for someone who found the pain caused by subcutaneous infusion intolerable or who found a central venous line burdensome." *See* FDA Mem. of Meeting Minutes, at 3 (Apr. 6, 2010) [FDA 1199]. Accordingly, on June 17, 2010, FDA granted orphan drug designation and recognized orphan drug exclusivity for Tyvaso in the treatment of PAH. *See* Letters from Timothy R. Coté, FDA, to Frank J. Sasinowski, Hyman, Phelps & McNamara, P.C. (June 17, 2010) [FDA 1214-18]. UTC's second period of exclusivity expired on July 30, 2016.

C. UTC Fails To Establish That Orenitram (Oral Treprostinil) Is Entitled To Orphan Drug Exclusivity

Before the expiration of UTC's orphan drug exclusivity for Tyvaso, the company began development of the drug at issue here, Orenitram, treprostinil in an extended-release oral tablet. On December 14, 2011, UTC requested orphan drug designation for Orenitram in the treatment of PAH. *See* Letter from Dean Bunce, United Therapeutics Corp., to Gayatri Rao, FDA (Dec.

14, 2011) [FDA 1-351]. In its request, UTC argued there was a plausible hypothesis of clinical superiority because Orenitram presented a major contribution to patient care in that the drug did not present the same limitations associated with an infusion pump (for subcutaneous and intravenous use) or a nebulizer (for inhaled use). *Id.* at 17-18 [FDA 18-19]. Instead, UTC argued, Orenitram was an oral tablet that is "simple, patient-friendly, and convenient." *Id.* at 18 [FDA 19]. On March 9, 2012, FDA issued a deficiency letter in response to UTC's orphan drug designation request for Orenitram. *See* Letter from Gayatri R. Rao, FDA, to Rex Mauthe, United Therapeutics Corp. (Mar. 9, 2012) [FDA 366-69].

On December 20, 2013, FDA approved Orenitram for the treatment of PAH. *See* Letter from Norman Stockbridge, FDA, to Dean Bunce, United Therapeutics Corp. (Dec. 20, 2013) [FDA 370-73]. Two years later (and four years after its original application), on December 7, 2015, UTC amended its designation request, offering three hypotheses for clinical superiority: "(A) that oral treprostinil has greater long-term efficacy than inhaled treprostinil; (B) that oral treprostinil's dosing flexibility provides greater safety in the target population versus Tyvaso; and (C) that oral treprostinil provides a MCTPC [major contribution to patient care] over Tyvaso because of the differential impact on patients' daily lives." *See* Letter from Frank J. Sasinowski, Hyman, Phelps & McNamara, P.C., to Gayatri R. Rao, FDA, at 6 (Dec. 7, 2015) [FDA 399].

On March 23, 2016, FDA responded to UTC's amended request and explained that because orphan drug designation typically covers the active moiety, not the formulation, Orenitram was covered under UTC's previous orphan drug designation for the active moiety treprostinil for use in the treatment of PAH.[12] *See* Letter from Gayatri R. Rao, FDA, to Frank J. Sasinowski, Hyman, Phelps & McNamara, P.C., at 1 (Mar. 23, 2016) [FDA 443-33]. FDA then

[12] *See supra* note 10.

carefully evaluated UTC's arguments in support of clinical superiority, and found them to be insufficient.[13] Among other things, the agency noted that because the adverse events listed in Orenitram's labeling appeared to be similar to those described in the Tyvaso labeling, UTC had not demonstrated greater safety over Tyvaso. *Id.* at 2 [FDA 444]. Nor had UTC addressed the complexities and inconveniences of administering drugs orally. For example, because Orenitram must be taken with food, a patient taking Orenitram must schedule his daily activities around when he has access to food with sufficient caloric and fat content. *Id.* at 2-3 [FDA 444-45]. The dosing schedule for Orenitram is also complex, such that some patients—particularly those who are mentally challenged or elderly—may have difficulty adhering to the schedule. *Id.* at 3 [FDA 445]. Accordingly, FDA found that UTC failed to demonstrate that Orenitram was entitled to orphan drug exclusivity. *See id.* [FDA 445].

D. Current Litigation

On August 4, 2017, UTC filed a complaint for declaratory and injunctive relief against the United States. The Complaint alleges that FDA "impermissibly denied Orenitram orphan drug exclusivity and required that UTC demonstrate that Orenitram is clinically superior to Remodulin and Tyvaso." Compl. ¶ 37. UTC thus alleges that "Defendants' denial of orphan drug exclusivity . . . was arbitrary and capricious, an abuse of discretion, exceeds Defendants' statutory authority, and is otherwise not in accordance with the law." *Id.*

[13] FDA's March 23, 2016 letter only addressed arguments UTC raised before the agency. Neither UTC's original application, nor its supplemental materials, presented FDA with the legal arguments it now raises in this lawsuit—namely, that Orenitram is automatically entitled to an additional exclusivity period upon approval and designation, and that the clinical superiority framework exceeds FDA's statutory authority. To the contrary, UTC acknowledged and accepted the applicability of the clinical superiority framework, and the company offered several hypotheses of clinical superiority.

The parties' motions for summary judgment followed. *See* Pl.'s Mot. J., Nov. 9, 2017, ECF No. 17.

ARGUMENT

I. STANDARD OF REVIEW

UTC has brought this case under the Administrative Procedure Act (APA). Pursuant to the APA, the Court may set aside agency action that is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law" or "in excess of statutory jurisdiction, authority or limitations, or short of statutory right." 5 U.S.C. § 706 (2)(A), (C). As part of its review, the Court must ensure that the agency "examine[d] the relevant data and articulate[d] a satisfactory explanation for its action," but may not "substitute its judgment for that of the agency." *Motor Vehicle Mfrs. Ass'n of the U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983) (citations and internal quotations omitted); *see also Am. Horse Prot. Ass'n v. Yeutter*, 917 F.2d 594, 596 (D.C. Cir. 1990) (court must "presume the validity of agency action") (citation omitted); *Cumberland Pharm. Inc. v. Food & Drug Admin.*, 981 F. Supp. 2d 38, 51 (D.D.C. 2013) ("The proper inquiry is not, then, whether there is sufficient evidence in the record to support the opposing conclusion, but rather whether the choice made by the agency has a rational basis in the evidence.") (citations and quotations omitted).

Where, as here, the agency's decision turns on the interpretation of a statute, courts apply the two-step framework articulated by the Supreme Court in *Chevron, USA., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984). Under this framework, a court must first determine "whether Congress has directly spoken to the precise question at issue. If the intent of Congress is clear, that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress." *Id.* at 842-43. But if the statute is silent or ambiguous on the specific issue, the court must defer to any agency interpretation that is

based on a permissible construction of the statute. *Id.* at 843; *Mayo Found. for Med. Educ. & Research v. United States*, 562 U.S. 44, 53 (2011) (an agency's construction is permissible "unless it is arbitrary or capricious in substance, or manifestly contrary to the statute") (citations and internal quotations omitted).

The *Chevron* framework applies no less to 5 U.S.C. § 706(2)(C) challenges, such as this one, where agency action is alleged to exceed statutory authority. It is well-established that challenges to a regulation as "'in excess of statutory jurisdiction, authority, or limitations, or short of statutory right,' 5 U.S.C. § 706(2)(C), are reviewed under the well-known *Chevron* framework." *Ass'n of Private Sector Colls. & Univs. v. Duncan*, 681 F.3d 427, 441(D.C. Cir. 2012) (citations omitted); *see also AstraZeneca Pharm. LP v. Food & Drug Admin.*, No. 12-472 (BAH), 2012 WL 1037457, at *2 (D.D.C. Mar. 28, 2012) ("To determine whether any agency exceeded its statutory authority, the court must engage in the two-step inquiry established by the Supreme Court in [*Chevron*].") (citation omitted).

Finally, a reviewing court "must give substantial deference to an agency's interpretation of its own regulations." *Thomas Jefferson Univ. v. Shalala*, 512 U.S. 504, 512 (1994); *Fed. Express Corp. v. Holowecki*, 552 U.S. 389, 397 (2008) (courts accept an agency's interpretation of its regulations unless the agency's position is "plainly erroneous or inconsistent with the regulation") (internal quotations omitted).

II. THE ORPHAN DRUG ACT DOES NOT MANDATE EXCLUSIVITY FOR ORENITRAM

UTC claims that, pre-FDARA, the Orphan Drug Act created a rigid formula. That formula, according to UTC, *required* FDA to recognize exclusivity for Orenitram (and thus extend UTC's prior monopoly in this area) once FDA designated and approved Orenitram as an orphan drug. But UTC misses an important ambiguity in the Orphan Drug Act's language—an ambiguity that becomes apparent when we apply that language to the facts of this case.

The relevant statutory provision, 21 U.S.C. § 360cc(a),[14] stated that (1) FDA's approval of an orphan-designated drug (2) shall preclude FDA from "approv[ing] another . . . such drug . . . until the expiration of seven years[.]" Before Orenitram, FDA approved and recognized exclusivity for Tyvaso—a drug with the same active ingredient. FDA, in fact, considers Orenitram and Tyvaso to be the same drug. UTC now requests exclusivity for Orenitram after the "expiration" of exclusivity it enjoyed on Tyvaso. And that naturally raises a question: is UTC permitted to renew a benefit that has already "expir[ed]" for that drug?

Here, the prior version of the Orphan Drug Act, which was in effect when UTC sought to designate Orenitram, provided no clear answer. Accordingly, FDA developed its own approach—one that has since been ratified by Congress.

A. Section 360cc Did Not Answer The Relevant Question

Section 360cc did not define what it meant for a drug's exclusivity to "expir[e]." On its face, the term can be understood in at least two different ways.

Under a narrow reading, the "expiration" of a drug's exclusivity could mean merely that FDA will stop recognizing exclusivity for a particular company's drug product, leaving the field open for the same (or different) company to obtain exclusivity when it develops another version of

[14] As noted previously, it is the pre-FDARA version of the Orphan Drug Act that governs this case.

the drug. Such a reading would create a race between companies to obtain their own seven years of monopoly—and, once one company secured approval, result in potentially limitless, sequential blocks of exclusivity for what is essentially the same drug. This is, in essence, the reading UTC advocates.

But "expiration" can also be read more broadly. That is, the "expiration" of a drug's exclusivity could mean the cessation of *all further* exclusivity protections—meaning that *no further bar* against the approval of subsequent "such drug[s]" is to be imposed. This second reading would foreclose FDA from recognizing exclusivity for other "such drug[s]," because the exclusivity on the drug had already expired.

Prior to the recent amendments, 21 U.S.C. § 360cc did not specify which of these readings Congress intended. And that ambiguity was compounded by another problem: Congress provided that orphan drug exclusivity would preclude FDA from "approv[ing] another . . . *such drug* . . . until the expiration of seven years," but did not define what it meant by the phrase "such drug." *See generally* 21 U.S.C. § 360cc; *cf. Baker Norton Pharm.*, 132 F. Supp. 2d at 36 (holding that the term "drug" as used in 21 U.S.C. § 360cc(a) is ambiguous). This omission was not trivial. Two drugs may have the same chemical structure; they may operate on the same physiological pathways; or they may have the same effects. Absent a clear definition of what makes one drug the same as another for purposes of section 360cc, it was impossible to know which drugs are affected by exclusivity—or by its "expiration." *See Genentech, Inc. v. Bowen*, 676 F. Supp. 301, 313 (D.D.C. 1987) (noting that the statute does not define what makes two drugs the same for purposes of 21 U.S.C. § 360cc); *Berlex Labs. Inc. v. Food & Drug Admin.*, 942 F. Supp. 19, 23 (D.D.C. 1996) (recognizing FDA's clinical superiority framework, and noting that "[t]he Orphan Drug Act is

silent as to the nature of the analysis FDA must undertake when deciding whether one drug is clinically superior to another").

The FDARA has now resolved these questions for future cases. Among other things, Congress has now clarified that exclusivity shall *not* be available to a drug that, in FDA's view, is the same as a drug that enjoyed exclusivity before. *See* FDARA, § 607(a)(3) [FDA 1884]. But this clarification only highlights the way the prior version of the statute, which governs this case, was ambiguous. And though the amendments indicate that Congress agreed with the idea that 21 U.S.C. § 360cc *should not* permit multiple exclusivity periods for the same drug, they do not definitively resolve whether, prior to this year, the Orphan Drug Act *did* in fact permit them.

Thus, the question remains—was exclusivity available to second-in-line drugs like Orenitram? No answer could be drawn from the statute's language alone.

B. FDA's Interpretation Is Reasonable

Because 21 U.S.C. § 360cc failed to resolve the relevant question, the task of interpreting the statute fell to FDA. Indeed, FDA had both the duty and the discretion to do so. *See, e.g.*, *Genentech*, 676 F. Supp. at 313 (noting that FDA is responsible for defining the scope of Orphan Drug Act exclusivity).

As the Supreme Court explained in *Chevron*, when a "statute is silent or ambiguous with respect to the specific issue," the agency has discretion to deal with the issue in any way that "is based on a permissible construction" of the statute's text. 467 U.S. at 842-43; *see also id.* at 843-44 ("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."). Absent "unambiguous statutory language to the contrary or unreasonable resolution of language that is ambiguous," the agency's "interpretation governs." *United States v. Eurodif S.A.*, 555 U.S. 305,

316 (2009); *see also id.* ("The whole point of *Chevron* is to leave the discretion provided by the ambiguities of a statute with the implementing agency.").

Exercising this discretion, FDA promulgated regulations to clarify the scope of orphan drug exclusivity. *See generally* 21 C.F.R. § 316.31 (defining "[s]cope of orphan-drug exclusive approval"); *id.* § 316.3 (defining various terms and provisions). Among other things, FDA interpreted exclusivity under 21 U.S.C. § 360cc to bar subsequent "approval . . . of the *same drug* product for the same use or indication for 7 years." 21 C.F.R. § 316.3(b)(12) (emphasis added). It defined "same drug" to mean "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," *unless* "the subsequent drug can be shown to be clinically superior to the first drug" (in which case, the two "will not be considered to be the same"). *Id.* § 316.3(b)(13)(i).

In practice, these regulations mean that FDA will recognize only *one* period of exclusivity for a drug—and will not recognize exclusivity in a way that would restrict approval of other "such" drugs *after* the "expiration of seven years." Specifically, FDA will recognize exclusivity to the *first* approved orphan-designated drug that contains a particular active ingredient. *See, e.g.*, 78 Fed. Reg. at 35,118 (noting the agency's "long-standing practice that a designated drug is eligible for orphan exclusive approval only if the same drug has not already been approved for the same use or indication"). A subsequent drug with the same active ingredient will be blocked by that exclusivity—and will not be eligible to obtain its own exclusivity—*unless* the sponsor can demonstrate that the drug is clinically-superior to the first (and therefore not the "same drug" under FDA's regulations). *See, e.g., Berlex Labs.*, 942 F. Supp. at 22 (recognizing that "[b]efore Avenox could be approved for the sale in the face of

Betaseron's exclusivity under the Orphan Drug Act, FDA also had to make a finding that Avenox was 'different' from Betaseron").

This rule reflects careful policy tradeoffs. *See* 57 Fed. Reg. at 62,077 [FDA 1792]. As FDA explained, the agency developed the regulations "by seeking as much as possible to protect the incentives of the Orphan Drug Act without allowing their abuse," and ultimately achieved "the best balance possible between protecting exclusive marketing rights and fostering competition." *Id*. [FDA 1792]; *see also* 78 Fed. Reg. at 35,127 [FDA 1830] (noting that multiple periods of exclusivity for the same drug would "be at odds with the Orphan Drug Act").

The alternative would be a regime where companies could "[o]btain infinite, successive 7-year periods of exclusivity," merely by making a series of minor modifications. Such a regime would run counter, and even undercut, the central purpose of the Orphan Drug Act—to incentivize drug development for otherwise "untreated patients." *See Genentech*, 676 F. Supp. at 312; *see also* H.R. Rep. 99-153, at 6-7 (June 3, 1985) [FDA 1762] ("The Committee hopes and anticipates that the amendment . . . will encourage the development of new orphan drugs for use in previously untreated rare diseases."). Indeed, if exclusivity were available to any sponsor who produces a new formulation of a previously approved orphan drug, regardless of whether it offers a meaningful benefit to patients, sponsors would have no reason to invest in developing other drugs. Rather, sponsors could make minor tweaks to existing orphan drugs with no material benefit to patients, knowing that they could extend their exclusivity and keep competition at bay, potentially indefinitely. Such a regime does not foster innovation or serve patients.[15]

[15] Notably, FDA's clinical superiority framework is also consistent with the Hatch-Waxman Amendments, which provide for abbreviated pathways for generic drugs. By contrast, allowing serial (and potentially infinite) exclusivity periods that would block generic drugs for rare diseases would run counter to those Amendments, and violate the general principle that

The upshot is that, under FDA's rules, UTC is *not* automatically entitled to receive exclusivity for Orenitram. Orenitram, an oral treprostinil drug, has the "same active moiety" as UTC's previously approved Tyvaso (inhaled treprostinil) and Remodulin (intravenous and subcutaneous treprostinil), both of which enjoyed their own exclusivity periods. In order for FDA to recognize exclusivity for Orenitram, UTC must show that Orenitram is clinically superior to—and therefore a different drug than—its predecessors. This UTC has not done. *See* Letter from Gayatri R. Rao, FDA, to Frank J. Sasinowski, Hyman, Phelps & McNamara, P.C., at 3 (Mar. 23, 2016) [FDA 445] (finding that UTC did not demonstrate clinical superiority of Orenitram over Tyvaso).

C. UTC's Challenges To FDA's Regulations Are Unavailing

UTC never actually engages with the full facts of this case, or what those facts mean in practice. Instead, UTC flatly denies any lack of clarity in the statute, and urges the Court to follow the *Depomed* decision, which held that the text of the Orphan Drug Act was unambiguous about the conditions for granting exclusivity and held that FDA's regulations were improper under *Chevron*'s first step. *See* Pl.'s Mot. J. at 14-15, 20-21. Respectfully, this Court should decline to follow that decision: its reasoning was flawed, and it should not be applied in this case.

In particular, the Court in *Depomed* did not appreciate that the "expiration" of exclusivity, as stipulated in 21 U.S.C. § 360cc, was both ambiguous and relevant to the conditions for recognizing exclusivity in the first instance (UTC repeats this error in its brief). *See generally Depomed*, 66 F. Supp. 3d at 229–33. To be sure, the Court did not have reason to

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monopolies should be construed narrowly. *See, e.g., Louisville Bridge Co. v. United States*, 242 U.S. 409, 417 (1917) ("[T]he universal rule that grants of special franchises and privileges are to be strictly construed in favor of the public right . . . .").

consider that issue directly. The plaintiff in *Depomed* was not seeking exclusivity for a drug similar to one that previously held exclusivity—or, put another way, the plaintiff was *not* seeking exclusivity after the "expiration" of that exclusivity for another "such drug." *See id.* at 223-24. Indeed, in its decision, the Court dismissed concerns about serial exclusivity as speculative. *See id.* at 235-37.[16] Here, of course, there is no need for speculation. UTC has already received fourteen years of orphan drug exclusivity for its treprostinil drugs, and is now seeking another seven years of exclusivity after its "expiration." These factual differences are reason enough not to follow *Depomed* here.

The Court's analysis in *Depomed* contained other errors as well. For example, the Court incorrectly concluded that conditioning exclusivity on a showing of clinical superiority is impermissible because the statute *already* included two exceptions to exclusivity, identified in 21 U.S.C. § 360cc(b). *See Depomed*, 66 F. Supp. 3d at 233. UTC repeats a similar argument in its brief. *See* Pl.'s Mot. J. at 14. But 21 U.S.C. § 360cc(b) enumerated two instances when FDA may disregard, or break, a previously-recognized exclusivity: (1) when the drug's sponsor cannot make sufficient quantities of a protected drug available, and (2) when the sponsor has waived its exclusivity. On its face, this provision spoke to the conditions for breaking a *previously-recognized* exclusivity. It did not address what made a drug *eligible for exclusivity* in the first instance, nor resolve what the "expiration" of exclusivity meant for future drugs.

The Court in *Depomed* also short-circuited the *Chevron* step-one analysis by focusing almost entirely on the statute's text without regard to its structure and purpose. *Chevron* directs

[16] Indeed, the district court found that the facts in *Depomed* were *sui generis* and thus that the "absurd" result of serial exclusivity "rarely, if ever, actually occurs." *Depomed*, 66 F. Supp. 3d at 236-37. This case—as well as the currently-pending *Eagle Pharmaceuticals, Inc. v. Burwell*, No. 16-0790 (D.D.C.) (Kelly, J.), which also raises issues of serial exclusivity—show that the court's prediction was overly optimistic.

courts to parse congressional intent using all the "traditional tools of statutory construction." 467 U.S. at 843 n.9; *Robinson v. Shell Oil Co.*, 519 U.S. 337, 341 (1997) ("The plainness or ambiguity of statutory language is determined by reference to the language itself, the specific context in which that language is used, and the broader context of the statute as a whole."); *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 669 (1990) (enlisting "the structure of the 1984 Act taken as a whole" to hold that the Hatch-Waxman Amendments are ambiguous); *see also Bell Atl. Tel. Cos. v. Fed. Commc'ns Comm'n*, 131 F.3d 1044, 1047 (D.C. Cir. 1997) ("The traditional tools include examination of the statute's text, legislative history, and structure . . . as well as its purpose."). Had the Court done so, it should have recognized that its reading of the statute conflicts with the Orphan Drug Act's structure and purpose, for all the reasons we articulated in the prior section.

Given these errors—and the factual differences between *Depomed* and this case—it was appropriate for FDA not to follow *Depomed* here. UTC repeatedly insinuates that this was somehow improper, but it is not. Respectfully, *Depomed* is one district court decision. It bound the agency in that particular case, but it does not indelibly bind the agency going forward or create any binding national precedent. Meanwhile, FDA was entirely transparent about its intentions going forward. After complying fully with the *Depomed* Court's order, FDA published a notice in the Federal Register announcing to all *future* parties that it would continue to follow its regulations. *See* 79 Fed. Reg. 76,888. FDA thus ensured that no one would be surprised by the approach the agency was taking, and reserved for another day the possibility of reassessing *Depomed*'s reasoning. This was an entirely proper course to take.

Putting *Depomed* to the side, UTC also claims that Congress's recent passage of the FDARA—which, for the first time, incorporated FDA's clinical-superiority standard into the

Orphan Drug Act—demonstrates that FDA did *not* have authority to impose that standard before. *See* Pl.'s Mot. J. at 6-7. In support of this argument, UTC points to the FDARA's "Rule of Construction." *Id.* That provision states that "[n]othing in the amendments . . . shall affect any determinations under [the exclusivity provision of the Orphan Drug Act] made prior to the date of enactment." [FDA 1885]. UTC reads this language to mean that the statute did not previously grant FDA authority to impose the clinical superiority framework. *See* Pl.'s Mot. J. at 6-7. But the FDARA's "Rule of Construction" actually *supports* FDA's interpretation. The only determinations under the exclusivity provision of the Orphan Drug Act made prior to the date of enactment are FDA's determinations *that already applied the clinical superiority framework.* The "Rule of Construction" expressly preserves those determinations from alteration, thus signaling that Congress viewed those determinations as legitimate and justified.

In this way, rather than undermining FDA's regulations, the FDARA actually *confirms* their validity. After all, Congress was aware of FDA's clinical superiority framework prior to the FDARA. *See* 79 Fed. Reg. at 76,888. If Congress had viewed that framework as improper, Congress could have abrogated or changed it. It did not do so. Instead, Congress expressly preserved FDA's decisions that relied on the framework—and then *expressly adopted* that framework wholesale into the statute going forward. In doing so, Congress indicated that it agreed with FDA's approach to exclusivity for orphan drugs. This type of agreement constitutes a ratification of the agency's prior interpretation,[17] and undermines both the reasoning and precedential value of *Depomed*. *See, e.g.*, *Porter v. Comm'r of Internal Revenue*, 856 F.2d 1205,

[17] *See, e.g.*, 21 U.S.C. § 355(j)(5)(B)(iv)(II)(dd)(AA) (incorporating tentative approvals for drugs into statutory scheme, which FDA had previously issued pursuant to 21 C.F.R. §§ 314.105(d), 314.107(b)(3)(v)); 21 U.S.C. § 371(h) (incorporating FDA's Good Guidance Practices under 21 C.F.R. § 10.115); 21 U.S.C. § 355(l)(1) (substantially incorporating provisions in FDA's disclosure regulation at 21 C.F.R. § 314.430(f)); 21 U.S.C. § 356 (substantially incorporating FDA's regulations at 21 C.F.R. §§ 314.500-314.560 for accelerated approval of new drugs for serious or life-threatening conditions).

1209 (8th Cir. 1988) ("Amending legislation is perceived as clarifying, not changing, an original statute's intended meaning when a conflict of statutory interpretation has arisen.") (citations omitted); *Duquesne Light Co. v. Envtl. Prot. Agency*, 698 F.2d 456, 467 (D.C. Cir. 1983) (noting that a technical statutory amendment reinforced the EPA's statutory interpretation); *see also Plaut v. Spendthrift Farm, Inc.*, 1 F.3d 1487, 1499 (6th Cir. 1993), *aff'd*, 514 U.S. 211 (1995) ("Where Congress disagrees with the manner in which the judiciary has interpreted a statute, it may amend that statute so as to effect the proper congressional intent, and thus render the faulty judicial interpretation moot.").

Simply put, the FDARA clarifies what should have always been evident: the old version of the Orphan Drug Act was ambiguous, and FDA properly interpreted that ambiguity to preclude the kind of automatic serial exclusivity that UTC seeks to achieve in this case. UTC's prior drugs received exclusivity because they were genuinely novel or offered a meaningful benefit to patients. Orenitram fails that test.

III. FDA PROPERLY APPLIED ITS CLINICAL SUPERIORITY FRAMEWORK

Turning away from the statutory argument, UTC also asserts that the manner in which FDA applied its clinical superiority framework was arbitrary and capricious. *See* Pl.'s Mot. J. at 16-20. As explained above, however, UTC did not demonstrate clinical superiority for its third treprostinil formulation, Orenitram, and UTC does not purport to challenge FDA's scientific conclusions regarding its failure to demonstrate clinical superiority in this lawsuit. Instead, UTC's application challenge rests on two arguments, that FDA's clinical superiority framework lacks definitional content and that FDA's application of the clinical superiority framework "treats similarly situated entities differently." *Id.* Neither argument has merit.

UTC's argument that "FDA never gave UTC a genuine opportunity to understand what is required for a showing of 'sufficient evidence' of clinical superiority," Pl.'s Mot. J. at 16, is unpersuasive. Indeed, UTC itself previously met this standard. *See* Letters from Timothy R. Coté, FDA, to Frank J. Sasinowski, Hyman, Phelps & McNamara, P.C. (June 17, 2010) [FDA 1214-18]. FDA's clinical superiority standard is set out in its regulations. Specifically, the regulations explain that a sponsor may demonstrate clinical superiority by showing that, as compared to the previously approved drug, its drug has a "significant therapeutic advantage" by providing greater effectiveness or safety or by making a "major contribution to patient care." 21 C.F.R. § 316.3(b)(3).

The regulations further explain that direct comparative clinical trials may be necessary to show greater effectiveness or safety, *see id.* § 316.3(b)(3)(i), (b)(3)(ii), and that to show greater safety, FDA applies a standard similar to the one applicable for claims in prescription drug labeling. *See id*. § 316.3(b)(3)(ii); 57 Fed. Reg. at 62,078 [FDA 1793]. For additional clarity, FDA provided an example of a change that could result in greater safety, namely, the elimination of an ingredient or contaminant that is associated with relatively frequent adverse events. *See* 21 C.F.R. § 316.3(b)(3)(ii). Clinical superiority by making a major contribution to patient care is reserved for "unusual cases." *Id.* § 316.3(b)(3)(iii); *see also* 57 Fed. Reg. at 62,077 [FDA 1792] (a major contribution to patient care "is not intended to open the flood gates to FDA approval for every drug for which a minor convenience over and above that attributed to an already approved orphan drug can be demonstrated"). The preamble to the Orphan Drug Regulations describes several factors, *e.g.*, convenient treatment location, duration of treatment, patient comfort, reduced treatment burden, advances in ease and comfort of drug administration, longer periods between doses, and potential for self-administration, that may bear on the agency's consideration

of whether a drug provides a major contribution to patient care. 57 Fed. Reg. at 62,079 [FDA 1794].

Nevertheless, UTC claims that the clinical superiority standard is unclear because FDA evaluates clinical superiority on a case-by-case basis. *See* Pl.'s Mot. J. at 17-18. But FDA routinely decides whether a sponsor's product-specific evidence meets general standards such as "safe" and "effective." *See, e.g.*, 21 U.S.C. § 355(d)(4), (d)(5). These types of scientific decisions are necessarily fact-specific, and the generality of the standards does not render them "fundamentally flawed." Rather, Congress entrusts expert agencies to make such decisions. *See PDK Labs. v. U.S. Drug Enforcement Admin.*, 438 F.3d 1184, 1194-95 (D.C. Cir. 2006) (interpreting *Pearson v. Shalala*, 164 F.3d 650 (D.C. Cir. 1999), to allow federal agencies to clarify a statutory term on a case-by-case basis).

Moreover, any argument that UTC was confused about the requirements, *see* Pl.'s Mot. J. at 16-19, is belied by the fact that just two years before seeking orphan drug designation for Orenitram, the company demonstrated clinical superiority for its second treprostinil formulation Tyvaso (inhaled treprostinil). *See* Letters from Timothy R. Coté, FDA, to Frank J. Sasinowski, Hyman, Phelps & McNamara, P.C. (June 17, 2010) [FDA 1214-18]. UTC knew how to prove clinical superiority because it had already done so for Tyvaso, and if UTC had any lingering questions about what was required to prove clinical superiority for Orenitram, UTC could have, as it did with Tyvaso, requested to meet with FDA to discuss those concerns.[18]

[18] Additionally, counsel representing UTC has filed requests under the Freedom of Information Act—including a request in 2010 for information about FDA's designation of Tyvaso—to understand how FDA applies its clinical superiority standard. UTC's counsel posts information on FDA's clinical superiority decisions on its blog. *See, e.g.*, *Orphan Drug Clinical Superiority: An Overview of Precedents Shows That MC-to-PC Clinical Superiority Is Not So Unusual* (Mar. 27, 2016), http://www.fdalawblog.net/2016/03/orphan-drug-clinical-superiority-an-overview-of-precedents-shows-that-mc-to-pc-clinical-superiority-/ (last visited Nov. 28, 2017); *A New "Greater Safety" Orphan Drug Clinical Superiority Precedent: PURIXAN (July*

In its motion for summary judgment, UTC also argues—for the first time—that FDA's application of the clinical superiority framework "treats similarly situated entities differently." Pl.'s Mot. J. at 16, 19-20. But UTC does not cite to any specific instance where FDA has treated similarly situated entities differently; moreover, UTC itself recognizes that an agency can treat parties differently if it "explain[s] the relevance of those [factual] differences to the purposes of the [underlying law]." *Id.* at 19 (citation omitted). The purpose of the Orphan Drug Act's exclusivity provision is to encourage the development of orphan drugs for use in "previously untreated rare diseases." H.R. Rep. 99-153, at 6-7 [FDA 1762]. FDA's clinical superiority framework achieves this purpose by granting exclusivity to the first drug sponsor or to a subsequent sponsor who is able to show that its drug is superior in a meaningful way, and thus a "different" drug. It does not, by contrast, award products that embody only marginal improvements to a previously approved drug. Thus, some sponsors are able to obtain exclusivity upon approval of a designated orphan drug and some are not, but those outcomes are consistent with the clinical superiority framework which permissibly implements a policy choice based on FDA's reading of the statutory text, structure, and purpose.

Accordingly, UTC's arguments regarding FDA's application of the clinical superiority framework are misplaced and unavailing.

5, 2016), http://www.fdalawblog.net/2016/07/a-new-greater-safety-orphan-drug-clinical-superiority-precedent-purixan-/ (discussing a "scorecard of precedents where FDA determined that an orphan drug is clinically superiority to another drug that is otherwise the same drug for the same orphan condition") (last visited Nov. 28, 2017).

CONCLUSION

For these reasons, we respectfully request that the Court deny UTC's motion for summary judgment, and enter summary judgment in favor of the United States.

Respectfully submitted,

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December 22, 2017

CERTIFICATE OF SERVICE

I hereby certify under penalty of perjury that on this 22nd day of December, 2017, a copy of the foregoing "DEFENDANTS' RESPONSE TO PLAINTIFF'S MOTION FOR SUMMARY JUDGMENT AND CROSS-MOTION" was filed electronically. This filing was served electronically to all parties by operation of the Court's electronic filing system.

s/ Alexander V. Sverdlov

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

UNITED THERAPEUTICS CORP.,	)	
Plaintiff,	)	Civil Action No. 1:17-cv-01577
v.	)	Judge Ellen S. Huvelle
UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES *et al.*,	)	
Defendants.	)	

[PROPOSED] ORDER

Upon consideration of the parties' cross-motions for summary judgment, as well as the administrative record submitted in this matter, it is hereby:

ORDERED that Plaintiff's motion for summary judgment is DENIED; and it is further

ORDERED that Defendants' motion for summary judgment is GRANTED; and it is further

ORDERED that judgment shall be entered for Defendants.

SO ORDERED.

Date: _____ _____

Hon. Ellen S. Huvelle
U.S. District Judge