

August 15, 2019

VIA ELECTRONIC SUBMISSION

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2019-P-1679; Braeburn, Inc. Response to July 24, 2019
Comments Submitted by Indivior Inc.

Dear Sir or Madam:

On behalf of Braeburn, Inc. (“Braeburn”), and in accordance with 21 C.F.R. § 10.30(g), the undersigned hereby submits supplemental information in support of Braeburn’s petition and in response to the comments submitted on July 24, 2019 by Indivior, Inc. (“Indivior”). Because Indivior’s comments fail to refute any of the statutory, regulatory or factual arguments raised in Braeburn’s Citizen Petition, and because *every* other comment submitted to the docket strongly endorses revoking orphan drug designation (“ODD”) for Sublocade™ (buprenorphine extended-release) injection, Braeburn hereby requests that the Food and Drug Administration (“FDA”) grant Braeburn’s petition immediately.

In its comments, Indivior does not dispute that Sublocade presently fails to satisfy either statutory test necessary to qualify as a *bona fide* orphan drug. Indivior admits, as it must, that opioid use disorder (“OUD”) currently afflicts millions of patients in the United States. And it does not deny that Sublocade is expected to be a highly profitable, blockbuster drug, or that Indivior already made hundreds of millions of dollars selling Subutex from 2002 to 2011, or that a significant portion of the funding to develop buprenorphine was sourced from the National Institutes of Health. But in Indivior’s view, these facts are unimportant under the law; that is, the facts simply do not matter. The only thing that matters is that Subutex (buprenorphine) was designated as an orphan drug nearly 25 years ago, and because buprenorphine is buprenorphine is buprenorphine, Sublocade should, *again*, get the benefit of that outdated FDA decision today.

But that is not what the law says – and certainly not what FDA’s regulations require. Those regulations clearly and unambiguously require the sponsor of a drug like Sublocade – a drug that is “otherwise the same” as a previously approved drug – to submit a *new* request for ODD in order to obtain orphan designation for the *new* drug. 21 C.F.R. § 316.20(a). This requirement ensures that the new drug (a) actually qualifies as a *bona fide* orphan drug, and (b) is potentially “clinically superior” to previously approved drugs containing the same active moiety. It also is intended to prevent inappropriate evergreening of both ODD and Orphan Drug Exclusivity (“ODE”). In essence, this requirement performs the same function in the ODD context that the statutory and regulatory “clinical superiority” requirement performs in the ODE context.

For decades, FDA interpreted and enforced its regulations in exactly this manner. But things appear to have changed in approximately 2016. For reasons FDA has never explained publicly, the Agency quietly adopted a new policy whereby it now automatically transfers ODD from one drug to another without requiring a new ODD request or a demonstration of potential clinical superiority, provided the same sponsor developed both products. For Sublocade, which was approved in late 2017, this policy change came just in the nick of time: as even Indivior appears to recognize, Sublocade could never have qualified as a *bona fide* orphan drug if it had been required to submit a new ODD request. Indivior Comments, at 12, 23-26 (July 24, 2019) (“Ind.”).

FDA’s new policy, however, is invalid because it conflicts with the clear language of FDA’s own regulations, as well as the language and intent of the Orphan Drug Act (“ODA”). This means that Sublocade’s ODD, which was granted solely on the basis of FDA’s new policy, is likewise invalid. Indeed, in its comments to the docket, Indivior confirms that it never submitted a new ODD request for Sublocade, never demonstrated that Sublocade presently satisfies the Patient Population or Cost Recovery prongs of the statute, and never presented a plausible hypothesis of clinical superiority under relevant *orphan drug standards*. Ind., at 23-26, 30-31. These admissions prove beyond a shadow of a doubt that Sublocade was never eligible for ODD in the first place. Its designation, therefore, must be revoked. 21 C.F.R. § 316.29(a)(3).

Indivior largely ignores the statutory and regulatory defects highlighted in Braeburn’s Citizen Petition and instead focuses the bulk of its comments on trying to resurrect the FDA’s grant of ODD to *Subutex* in 1994. Professing that this is “Braeburn’s central charge,” Indivior throws up a historical smokescreen 22 pages long. This tactic is not surprising, since Indivior has no valid response to any of Braeburn’s more central statutory or regulatory arguments. But its defense of the 1994 ODD decision is equally inadequate. Try as it might, Indivior cannot hide the fact that the “estimates and justifications” it provided to FDA for cost recovery purposes in 1993 were obviously very different than the estimates and predictions it was relying upon to run its business in 1993. And the fact that Indivior’s submission to FDA contained mostly estimates cannot salvage the situation: a regulatory requirement to provide estimates does not give a sponsor free rein to provide *inaccurate* estimates that omit *material information*. Yet, it appears this is exactly what Indivior did in 1993 (and, surprisingly, failed to correct in 2000 and 2002).

Consequently, for the reasons set forth below and in Braeburn’s Citizen Petition, FDA should revoke the ODD that currently applies to Sublocade, and concomitantly revoke or refuse to grant ODE to Sublocade, pursuant to 21 C.F.R. § 316.29. Such action is necessary to prevent Indivior from perpetrating an historic abuse of the Orphan Drug Act. More importantly, and as reflected in many of the comments submitted to docket, such action is critical for the protection of vulnerable patients suffering from opioid addiction, who need new and innovative treatment options to combat the ongoing opioid crisis.

I. Sublocade Is Not Eligible for ODD Under the Orphan Drug Regulations

FDA should revoke the ODD for Sublocade because Indivior has now confirmed it never submitted a new designation request containing a “plausible hypothesis” that Sublocade is superior to previously approved buprenorphine products. As a result, Sublocade was never eligible for ODD under FDA’s regulations. 21 C.F.R. § 316.29(a)(3).

A. FDA Regulations Required Indivior to Submit a New ODD Request for Sublocade

FDA’s regulations are clear and unambiguous: if a drug is “otherwise the same” as a previously approved drug for the same rare disease or use, a sponsor cannot “seek or obtain” ODD unless it presents a “plausible hypothesis” that the new drug “may be clinically superior to the first drug.” 21 C.F.R. § 316.20(a). If the sponsor fails to submit a “medically plausible hypothesis for the possible clinical superiority of the subsequent drug,” FDA must refuse to grant a request for ODD. *Id.* § 316.25(a)(3). These regulations apply broadly to any sponsor of a drug that is “otherwise the same as an already approved drug.” *Id.* § 316.20(a). Significantly, there is no exception whatsoever for a sponsor who developed both the new drug and the “already approved” version. By its express terms, therefore, this regulatory requirement clearly applies to Indivior and Sublocade.

In its comments, Indivior admits that it never submitted a new ODD request for Sublocade but argues that it was not required to do so because “orphan designation attaches to active moieties,” not particular products, and because “Indivior already held a lawfully granted orphan designation for buprenorphine as an OUD treatment.” Ind., at 29. But this is no answer at all. As Braeburn previously explained, even if Sublocade and Subutex are considered to be the “same drug” because they contain the same active moiety, *FDA’s regulations, by their express terms, apply to this very situation*. Specifically, those regulations require the submission of a new ODD request containing a plausible hypothesis of clinical superiority whenever one drug is “otherwise the same” as a previously approved drug.

FDA explained as recently as 2013 that “[i]n the absence of a clinical superiority hypothesis, the Agency does not interpret the Orphan Drug regulations to permit designation of a drug that is otherwise the same as a drug that is already approved for the same use. . . .”¹ FDA further explained that this requirement is necessary to (1) further the “primary purpose of the Orphan Drug Act, which is to provide incentives to develop promising drugs for rare diseases or conditions *that would not otherwise be developed[;]*”² and (2) prevent “inappropriate ‘evergreening’ of exclusive approval periods.”³ Moreover, FDA recognized that both of these concerns exist when the same sponsor develops both products, particularly concerns about inappropriate evergreening. Indeed, the example provided by FDA in the preamble to its proposed regulations specifically involved a single sponsor. It is thus clear that FDA interpreted this regulation in 2013 as applying to all sponsors, consistent with the goals of the ODA. It thus would

¹ 78 Fed. Reg. 35117, 35122 (June 12, 2013).

² *Id.* (emphasis added).

³ 76 Fed. Reg. 64868, 64870 (Oct. 19, 2011).

not be reasonable to interpret the regulations now to apply only when the new and “previously approved” products are developed by different sponsors.

Indivior nevertheless appears to believe that the “same drug” regulation overrides the “plausible hypothesis” regulation. Ind., at 29. But this interpretation ignores the fact that the “plausible hypothesis” regulation explicitly references and incorporates the “same drug” regulation by requiring a new ODD submission, and a demonstration of potential clinical superiority, whenever a sponsor seeks ODD for a drug that is “otherwise the same” as a previously approved drug. 21 C.F.R. § 316.20(a). In this way, the regulations work in tandem to prevent inappropriate evergreening and ensure that only *bona fide* orphan drugs receive designation. In other words, by requiring a demonstration of potential clinical superiority, the “plausible hypothesis” regulation operates in the ODD context in exactly the same way the “clinical superiority” provisions (both statutory and regulatory) works in the ODE context. Indivior’s interpretation, by contrast, contravenes the intent of the Orphan Drug Act and the regulations by opening up a gaping loophole for evergreening and providing unnecessary incentives to drugs that are not *bona fide* orphan drugs.⁴ Not surprisingly, Indivior is attempting to take advantage of that loophole here by evergreening its ODD and ODE for Sublocade, despite the ongoing opioid crisis and to the clear detriment of opioid patients and the public health.

B. Sublocade Was Granted ODD Pursuant to a New FDA “Automatic Transfer” Policy

Seeking to evade this conclusion, Indivior next argues that the regulations do not mean what they clearly say, *i.e.*, that the regulations do not require a new ODD request for drugs like Sublocade that are the “same” as a previously approved drug. According to Indivior, FDA’s regulations and practice have always incorporated an automatic ODD transfer policy, so Indivior finds it “puzzling” that Braeburn would believe otherwise. Ind., at 23-24. Indivior thus asserts that FDA is treating Sublocade consistently with similarly situated drugs and in accordance with its “longstanding orphan-drug regulations” that have been in place “for decades.” Ind., at 24.

But Indivior provides little support for its theory other than its own bald assertions, which recent events have demonstrated are a dubious source at best.⁵ In fact, the only evidence Indivior cites is an FDA letter dated March 23, 2016. Ind., at 24. This, of course, represents the relatively recent occasion when FDA changed its interpretation and adopted its new automatic transfer policy (or at least communicated that new policy to a member of the regulated industry). It is telling that Indivior does not identify a single earlier example or precedent to support its argument.

⁴ See *Genentech, Inc. v. Bowen*, 676 F. Supp. 301, 312 (D.D.C. 1987) (“The legislative history is replete with references to the fundamental need to provide treatment for presently untreated patients.”) (emphasis added).

⁵ In April 2019, a federal grand jury in Virginia indicted Indivior for fraudulently marketing a prescription opioid. The Justice Department alleges that Indivior made “false and misleading claims” to physicians, pharmacists, and others over the course of many years. See Department of Justice Press Release, *Indivior, Inc. Indicted for Fraudulently Marketing Prescription Opioid* (April 9, 2019), available at <https://www.justice.gov/opa/pr/indivior-inc-indicted-fraudulently-marketing-prescription-opioid>. Yesterday, federal prosecutors issued a superseding indictment accusing the company of intentionally lying to physicians, pharmacists, FDA, other federal regulators about the risks of accidental exposure to children posed by Suboxone Film. Law360, DOJ Takes Another Shot at Suboxone Film Fraud Case (Aug. 14, 2019), available at <https://www.law360.com/governmentcontracts/articles/1188833/doj-takes-another-shot-at-suboxone-film-fraud-case> (subscription required).

Braeburn, of course, identified two relevant precedents – Nutropin Depot® (1999) and Tyvaso® (2010) – demonstrating that the regulations *were* interpreted and applied differently by the relevant FDA officials since at least the late 1990s and that FDA’s automatic ODD transfer policy is new. Indivior attempts to dismiss those examples as irrelevant, but its objections are frivolous. Moreover, Braeburn has now identified a third, more recent example – glatiramer acetate (discussed below) – demonstrating that FDA’s automatic ODD transfer policy is, in fact, new – and markedly different than FDA’s past interpretation of the regulations.

Indivior attempts to dismiss the Nutropin Depot example on the purported basis that “the Agency’s decision neither references the earlier Nutropin product or the identity of its NDA holder.” Ind., at 25 n.6. But this assertion is categorically false. The Agency decision specifically references “Table 1,” which is a list of “FDA Approved Human Growth Hormones,” and Table 1 clearly identifies (1) the freeze-dried formulation of *Nutropin*® as a relevant, previously approved product, and (2) *Genentech* as the sponsor of Nutropin (the same sponsor as for Nutropin Depot).⁶ Nutropin was granted ODD in 1987⁷ and approved prior to Nutropin Depot, so the Nutropin Depot example reconciles perfectly with Sublocade and provides strong support for Braeburn’s position that FDA has adopted a new, informal ODD transfer policy. Indivior apparently overlooked Table 1 when preparing its comments.

Indivior next seeks to undermine the Tyvaso example on the purported basis that Tyvaso “automatically” was entitled to orphan designation based on FDA’s prior orphan designation of treprostinil,” not upon any requirement to present a plausible hypothesis of clinical superiority. Ind., at 24, n. 6 (emphasis added). But Indivior’s evidence is again wafer-thin: a single, cherry-picked sentence that is taken completely out of context. And once again, Indivior overlooks critical information that clearly and unequivocally contradicts its assertion. In a later passage in the very same document, FDA states:

in order to be eligible for orphan drug designation as a different drug from the parenteral treprostinil, it only needed to be shown that inhaled treprostinil [Tyvaso] was *clinically superior* to the approved parenteral treprostinil [Remodulin] ... for the treatment of pulmonary arterial hypertension.”⁸

In other words, the very document Indivior cites states that FDA’s grant of ODD to Tyvaso was based upon a clinical superiority finding, not an “automatic” ODD transfer.

But that is not the only evidence Indivior ignores. Indivior’s assertion also is belied by the subsequent statements and actions of United Therapeutics Corporation (“UTC”), the sponsor of Tyvaso, the FDA, and the law firm that represented UTC in that matter (which happens to be the same law firm that represents Indivior in this matter). In a December 14, 2011 letter to FDA, for example, UTC described the Tyvaso ODD decision this way:

⁶ See Braeburn Citizen Petition, Docket No. FDA-2019-P-1679, Exh. 13, p. 6 (April 6, 2019) (“Braeburn CP”).

⁷ FDA Orphan Drug Database, Nutropin and Nutropin Depot (Exhibit 1).

⁸ Ind., Ex. J, p. 5.

On June 17, 2010, OOPD designated UTC's inhaled treprostinil, marketed as Tyvaso, for the treatment of patients with PAH *after determining that the inhaled version is not the "same drug" as the previous approved versions of the drug, because it is "clinically superior" (greater safety).*⁹

Clearly, UTC officials did not subscribe to the fiction Indivior is now peddling that Tyvaso was granted ODD "automatically" without a showing of clinical superiority.

Nor did FDA. In its brief filed in a subsequent lawsuit with UTC, FDA explained its ODD decision for Tyvaso this way:

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. . . .* Accordingly, on June 17, 2010, FDA granted orphan drug designation and recognized orphan drug exclusivity for Tyvaso in the treatment of PAH.¹⁰

Likewise, when UTC's law firm submitted a response on December 7, 2015 to FDA's denial of ODD for Orenitram (UTC's third treprostinil product), it never argued that ODD should be transferred "automatically." Instead, the firm argued that Orenitram was eligible for ODD because there was a plausible hypothesis that it was clinically superior to UTC's two previously approved treprostinil products (*i.e.*, Remodulin and Tyvaso).¹¹ It strains credulity to believe that this highly skilled law firm, with deep expertise on orphan drug issues, would not have mentioned the possibility of "automatic" ODD transfer if it was such a well-established and longstanding policy, as members of that same law firm now contend on behalf of Indivior. Indivior's law firm, of course, is free to adopt a new legal theory when arguing on behalf of a new client in a different matter; but it has no special powers to single-handedly change historical facts. The undeniable facts here, of course, are that FDA's automatic ODD transfer policy was not applied in the Tyvaso case and is not well-established and longstanding. And no amount of "cherry-picking" by Indivior will make it so.

The Nutropin Depot and Tyvaso examples thus remain unsullied by Indivior's clumsy attacks. Moreover, those examples are further buttressed by a third, more recent precedent just identified by Braeburn. In December 2013, FDA officials describing the regulatory history of glatiramer acetate ("GA") stated that "this orphan designation **expired** on December 20, 2003,"¹² the exact same date that ODE for the previously approved 20 mg/vial version of GA expired. As

⁹ UTC Request for ODD for Orenitram, p. 17 (Dec. 14, 2011) (emphasis added) (Exhibit 2).

¹⁰ See Def.'s Response to Pl.'s Mot. Summ. J. and Cross-Mot., *United Therapeutics Corp. v. HHS*, Civ. Action No. 17-1577, p. 12 (Dec. 22, 2017) (Braeburn CP, Exh. 1). FDA also stated that UTC was not "technically required" to submit a request for ODD because of the prior designation of Remodulin (treprostinil). FDA Brief, p. 10 n. 10. But that statement was made after FDA changed its policy. While it thus might reflect FDA's current policy, it does not describe the policy that FDA actually applied to Tyvaso in 2010.

¹¹ See Letter from Frank J. Sasinowski, Hyman, Phelps & McNamara to Gayatri R. Rao (Dec. 7, 2015) (Exhibit 3).

¹² See Memorandum from Pediatric and Maternal Health Staff to Division of Neurology Products (NDA 20622), p. 2 (Dec. 22, 2013) (emphasis added) ("GA Memorandum") (Exhibit 4).

a result of this ODD “expiration,” FDA did not automatically grant ODD to the 40 mg/mL version of GA, which was subsequently approved on January 28, 2014. Like Sublocade, the 40 mg/mL version of GA contained the same active moiety as a previously approved drug product developed by the same company.

This is the first example we have identified where FDA described and treated an ODD period as “expired.” In its original Citizen Petition submission, Braeburn requested that FDA do exactly that with respect to Sublocade. Braeburn CP, at 11. Braeburn thus renews that request now in light of this important new precedent (see section II below).

Together, these precedents paint a clear picture of FDA’s interpretation of its ODD regulations prior to approximately 2016. Specifically, FDA required all sponsors of drugs that otherwise were the same as a previously approved drug to submit a new ODD request presenting a plausible hypothesis of clinical superiority in order to obtain ODD. *See* 21 C.F.R. § 316.20(a). This requirement applied not just to new sponsors but also to sponsors who owned both the new product and the previously approved product. For the reasons described herein, Braeburn believes this longstanding policy is appropriate and, in fact, is the *only* reasonable interpretation of the ODD regulations.

C. FDA New “Automatic ODD Transfer” Policy Conflicts With Its Clear and Unambiguous Regulations, Is Arbitrary and Capricious and Procedurally Defective

At some point in approximately 2016, FDA reversed course and adopted an “automatic ODD transfer” policy for drugs developed by the same sponsor. Moreover, it did so without formal notice and without providing any opportunity for public comment.¹³ Because FDA’s new policy conflicts with the clear language of the FDA regulations, is otherwise arbitrary and capricious, and was not promulgated via notice-and-comment rulemaking as required by the Administrative Procedure Act (“APA”), it is invalid and cannot be applied to Sublocade.

Although reviewing courts often defer to an agency’s interpretation of its own ambiguous regulations, “the possibility of deference can arise only if a regulation is genuinely ambiguous … after a court has resorted to all the standard tools of interpretation.”¹⁴ This requires a careful consideration of the “text, structure, history, and purpose of a regulation.”¹⁵ “But if the law gives an answer – if there is only one reasonable construction of a regulation – then a court has no business deferring to any other reading, no matter how much the agency insists it would make more sense.”¹⁶ In this case, there is only one reasonable interpretation of FDA’s orphan drug regulations – the one adopted and applied in the Nutropin Depot, Tyvaso and GA precedents.

¹³ As noted in Braeburn’s Petition, FDA’s website briefly mentions this policy but provides no explanation or justification for the change in policy. Braeburn CP, p. 6.

¹⁴ *Kisor v. Wilkie*, No. 18-15, slip op. at 11 (U.S. June 26, 2019).

¹⁵ *Kisor*, No. 18-15, slip op. at 14.

¹⁶ *Kisor*, No. 18-15, slip op. at 13; *see also Christiansen v. Harris County*, 529 U.S. 576, 588 (2000) (“*Auer* deference is warranted only when the language of the regulation is ambiguous.”).

The most important factor in determining the meaning of a regulation is the regulatory language itself. Here, the regulatory language is clear and unambiguous and requires the submission of a new ODD request (including a plausible hypothesis of clinical superiority), without exception, whenever a sponsor is seeking ODD for a new drug that is otherwise the same as a previously approved drug. 21 C.F.R. § 316.20(a). The regulation does not contain any exceptions to this general rule so there is no basis for FDA to recognize an unwritten exception where a sponsor develops both drug products at issue.¹⁷ On the contrary, such an exception would ignore and nullify the “otherwise the same” language in the regulation.¹⁸ Moreover, it would undercut the primary purpose of the regulation – and of the Orphan Drug Act itself – to prevent inappropriate evergreening and to ensure that orphan drug incentives are available only to *bona fide* orphan drugs that help develop promising drugs for rare diseases or conditions *that would not otherwise be developed*.¹⁹ As FDA recognized in 2011, the risk of inappropriate evergreening is particularly acute where both drugs are developed by the same sponsor, as is the case here.²⁰

Even if the regulations were ambiguous (which they are not), FDA’s new “automatic ODD transfer” interpretation would still fail because it is not reasonable. Among other things, it fails to establish reasonable time limits between ODD transfers. As Braeburn pointed out in its Citizen Petition, FDA is allowing Sublocade to piggy-back on a designation decision that is *almost 25 years old*. Under FDA’s new policy, there is nothing to prevent similar ODD transfers for drugs approved 50, 100 or even 500 years from now. This is inherently unreasonable and will create ODD “perpetuities” that provide permanent benefits to their holders regardless of whether the future products qualify as *bona fide* orphan drugs. Likewise, FDA’s new interpretation fails to ensure that new drug products subject to an ODD transfer continue to meet the qualifications as a *bona fide* orphan drug. This is necessary to ensure that the benefits of ODD and ODE accrue only to drugs that otherwise would not be developed, which FDA itself recognizes is the primary purpose of the Orphan Drug Act.²¹

The fact that FDA’s new interpretation reverses decades of precedent, creates “unfair surprise” to regulated parties like Braeburn, and was never formally or authoritatively announced to the regulated industry also renders that interpretation arbitrary and capricious.²² Furthermore, it strongly undercuts any claim FDA might have for *Auer* deference from a reviewing court.²³ The Supreme Court has expressed particular concern about the “disruption of expectations [that] may

¹⁷ *Stat-Trade, Inc. v. FDA*, 869 F. Supp. 2d 95, 105 (D.D.C. 2012) (holding that FDA could not add a limitation to clear statutory provisions that applied in defined circumstances without the limitation imposed by FDA).

¹⁸ An interpretation of a statute or regulation that renders any provision inoperative and superfluous contravenes well established rules of statutory construction and must be rejected. *See Milner v. Dept. of Navy*, 131 S. Ct. 1259, 1268 (2011); *Edison Elec. Inst. v. EPA*, 996 F.2d 326, 335 (D.C. Cir. 1993) (applying “the elementary canon of construction that a statute should be interpreted so as not to render one part inoperative”) (citation omitted); *FTC v. Manager, Retail Credit Co.*, 515 F.2d 988, 994 (D.C. Cir. 1975) (“The presumption against interpreting a statute in a way which renders it ineffective is hornbook law.”).

¹⁹ 76 Fed. Reg. 64868, 64870.

²⁰ *Id.*

²¹ 78 Fed. Reg. 35117, 35122; 76 Fed. Reg. 64868, 64870; *Genentech, Inc. v. Bowen*, 676 F. Supp. 301, 312.

²² *Smiley v. Citibank, NA*, 517 U.S. 735, 742 (1996) (“Sudden and unexplained change … or change that does not take account of legitimate reliance on prior interpretation … may be ‘arbitrary and capricious [or] an abuse of discretion,’ 5 U.S.C. § 706(2)(A).”)

²³ *Auer v. Robbins*, 519 U.S. 452 (1997).

occur when an agency substitutes one view of a rule for another.”²⁴ The Court thus has observed that it has “rarely given *Auer* deference to an agency construction ‘conflict[ing] with a prior one.’”²⁵ In this case, as demonstrated conclusively above (see sections I.A and I.B), FDA’s new interpretation of 21 C.F.R. § 316.20(a) sharply conflicts with its prior interpretation, thereby creating unjustified and unfair surprise to regulated companies like Braeburn.

Finally, because FDA’s ODD regulations are clear and unambiguous, the Agency must apply them as written and in a manner that is consistent with previous FDA decisions for Nutropin Depot, Tyvaso and GA.²⁶ This means FDA must refuse to grant ODD to drugs that are otherwise the same as a previously approved drug unless the sponsor submits a new ODD request containing a plausible hypothesis of clinical superiority. Moreover, this requirement must be applied to drugs like Sublocade where the same sponsor developed both drugs at issue.

If FDA wants to change this requirement to implement an “automatic ODD transfer” policy, it must do so through notice-and-comment rulemaking. FDA’s “plausible hypothesis” regulation, which was published in the Federal Register after notice-and-comment rulemaking,²⁷ unquestionably is a “legislative rule.”²⁸ While FDA certainly retains authority to change or revise that regulation, to do so, it “must comply with the Administrative Procedure Act (APA), including its requirements for notice and comment.”²⁹ FDA’s implementation of a new “automatic ODD transfer” policy without going through notice-and-comment rulemaking thus violates the Administrative Procedure Act, 5 U.S.C. § 553, and is invalid. Until FDA formally revises its regulation, it must apply the “plausible hypothesis” regulation as written, *i.e.*, to apply even where both drugs at issue are developed by the same sponsor.

D. Indivior Failed to Comply With FDA’s ODD Regulations

For all of these reasons, Sublocade was not eligible for ODD unless Indivior complied with FDA regulations at 21 C.F.R. § 316.20(a) by submitting a new ODD request that included both (1) a demonstration that Sublocade is a *bona fide* orphan drug under either the Cost Recovery or Patient Population prongs, and (2) a plausible hypothesis that Sublocade is clinically superior to previously approved buprenorphine products. Indivior has admitted it did not do so, which should be the end of the matter: FDA must revoke Sublocade’s ODD.

²⁴ *Kisor*, No. 18-15, slip op. at 18.

²⁵ *Kisor*, No. 18-15, slip op. at 18.

²⁶ *FCC v. Fox Television Stations, Inc.*, 556 U.S. 502, 515 (2008) (“An agency may not, for example, depart from a prior policy *sub silentio* or simply disregard rules that are still on the books.”).

²⁷ 57 Fed. Reg. 62076 (Dec. 29, 1992).

²⁸ *American Mining Congress v. MSHA*, 995 F.2d 1106, 1109 (D.C. Cir. 1993) (a rule is likely a legislative rule if, among other things, it is published in the Federal Register).

²⁹ *Clean Air Council v. Pruitt*, 862 F.3d 1, 8-9 (D.C. Cir. 2017); see also *Perez v. Mortgage Bankers Ass ’n*, 135 S. Ct. 1199, 1206 (2015) (“[T]he D.C. Circuit correctly read § 1 of the APA to mandate that agencies use the same procedures when they amend or repeal a rule as they used to issue the rule in the first instance.”); *Nat ’l Family Planning & Reproductive Health Ass ’n, Inc. v. Sullivan*, 979 F.2d 227,234 (D.C. Cir. 1992) (“[A]n agency issuing a legislative rule is itself bound by the rule until that rule is amended or revoked [and] may not alter [such a rule] without notice and comment.”); *Shalala v. Guernsey Memorial Hospital*, 514 U.S. 87, 100 (1995) (APA rulemaking would be required if an interpretive rule “adopted a new position inconsistent with any of the [Agency’s] regulations.”).

Apparently recognizing the weakness of its position, Indivior contends that it did, in fact, provide FDA with a “plausible hypothesis” of clinical superiority. Ind., at 29. This plausible hypothesis, however, allegedly was submitted as part of the Sublocade NDA, not in any new ODD request. Ind., at 29. There are thus three major fallacies with Indivior’s contention. First, under FDA’s regulations, a “plausible hypothesis” must be submitted as part of an ODD request, 21 C.F.R. § 316.20(a),³⁰ and an ODD request, by statute, must be submitted “before the submission of an application under section 505(b) for the drug.” 21 U.S.C. § 360bb(a)(1). Indivior’s “plausible hypothesis” submission was therefore invalid because Indivior did not submit it in the appropriate form (ODD request) or within the applicable deadline (*prior* to NDA submission).

Second, because it was not submitted in a new ODD request as required by the regulations, there is no evidence that the FDA officials specifically authorized to make ODD decisions ever reviewed Indivior’s plausible hypothesis “submission” or determined that Indivior had satisfied the applicable standards *under the Orphan Drug Act*. Indivior asserts that FDA agreed with its “plausible hypothesis” theory when it assigned Priority Review to its NDA. Ind., at 30. While the standards for priority review and a “plausible hypothesis of clinical superiority” may be similar, they are not the same, nor can these separate decisions be made by the same FDA officials. Under FDA policy, priority review decisions are made by the review division “with concurrence from the division director.”³¹ ODD decisions, by contrast, must be made by the Director of the Office of Orphan Products Development (“OOPD”).³² In this case, there is no evidence that the Director of OOPD ever reviewed or confirmed Indivior’s “plausible hypothesis” argument. FDA’s Priority Review process thus is not a valid substitute for OOPD review.

Finally, Indivior never demonstrated in a new ODD request that Sublocade is a *bona fide* orphan drug under either the Cost Recovery or Patient Population prongs of the ODA. See 21 U.S.C. § 360bb(a)(2). This, of course, is because Sublocade does not currently qualify as a *bona fide* orphan drug, and never did: OUD affects millions of patients, and Sublocade is expected to be a “blockbuster” drug generating peak annual revenue of approximately \$1 billion. Accordingly, Indivior did not “fully compl[y]” with the orphan drug regulations or the “plausible hypothesis” requirement. As such, it was never entitled to ODD in the first place, and its designation must now be revoked.

II. Sublocade Is Not Eligible for ODD Under the Orphan Drug Act

In its Petition, Braeburn argued that Sublocade is not eligible for ODD under the Orphan Drug Act because, among other things, FDA’s automatic ODD transfer policy violates the statute when applied in the specific context of the Cost Recovery Prong. See Braeburn CP, at 12. Even though the statute requires FDA to consider all sales in the United States of “such drug” without time limitation, 21 U.S.C. § 360bb(a)(2)(B), FDA’s cost recovery analysis was limited to the first seven years of expected sales of Subutex and thus did not account for any sales of Sublocade.

³⁰ The regulations provide that a sponsor may “seek and obtain” ODD if it can present a plausible hypothesis of clinical superiority. 21 C.F.R. § 316.20(a). The regulations thus provide no way to establish a plausible hypothesis of clinical superiority other than by “seek[ing]” ODD by submitting a request under 21 C.F.R. § 316.20(a).

³¹ FDA, Manual of Policies & Procedures (MAPP) 6020.3 Rev. 2 (June 25, 2013), available at <https://www.fda.gov/media/72723/download>.

³² FDA, Staff Manual Guide 1410.901 (Jan. 6, 2011), available at <https://www.fda.gov/media/81989/download>.

Braeburn argued that FDA cannot apply ODD determinations broadly and without time limitation to any future drug that contains the same active moiety while simultaneously limiting the cost recovery analysis to only seven years. If FDA limits the cost recovery analysis to the first seven years of sales, then ODD likewise must be limited to the specific “such drug” covered by that assessment (*i.e.*, Subutex).

Although Indivior did not specifically address this argument in its comments, it nevertheless observed that the seven-year time limitation established in FDA’s cost recovery regulations “aligns the cost-recovery provision with the ODE reward, which likewise provides seven years of marketing exclusivity.” Ind., at 5. Braeburn agrees with this analysis and believes it provides additional support for limiting ODD granted under the Cost Recovery prong to the specific drug that enjoys the concomitant ODE period. Specifically, to ensure the cost recovery provision is fully aligned with the seven-year ODE reward, ODD should expire, at the latest, at the same time ODE expires (as FDA confirmed in its GA decision discussed above). In this case, buprenorphine’s ODD thus should have expired in 2009.

There is ample precedent for FDA to impose an expiration date on ODDs. In its Petition, Braeburn pointed out that FDA’s longstanding policy has been that ODE is “used up” or “spent” if the same drug already has been approved for the same orphan indication and argued that FDA should apply that same policy to ODD. Braeburn CP, at 11. Braeburn recently learned that FDA appears to have done just that in 2013 with respect to GA. As discussed in more detail above, FDA specifically determined that GA’s orphan designation “expired” on the same date as its ODE.³³ The Nutropin Depot and Tyvaso examples also can be viewed as examples of FDA determining that the original ODD period was “used up,” “spent,” or just plain “expired,” thereby requiring submission of a new ODD request for subsequent versions of the drug.

Indivior nevertheless suggests that FDA cannot implement an ODD expiration policy because it is not authorized by the statute or regulations. Ind., at 28. But that assertion is erroneous: FDA’s existing regulation requiring a “plausible hypothesis of clinical superiority” serves that function quite nicely, particularly since it is the ODD version of the “clinical superiority” requirement applicable to ODE determinations. *See* 21 C.F.R. § 316.20(a). Both provisions, in fact, are intended to protect against evergreening by ensuring that ODD and ODE are not awarded serially to the “same” drug. Both provisions, in other words, trigger the “expiration” of the original ODD or ODE period by requiring a new demonstration of clinical superiority for any drug that is otherwise the “same” as a previously approved drug. Moreover, because the “plausible hypothesis” regulation was promulgated by FDA under specific authority granted by the Orphan Drug Act, 21 U.S.C. § 360bb(d), it is not subject to the same legal infirmity as FDA’s “clinical superiority” regulation, which was successfully challenged in the *Eagle* and *Depomed* cases.³⁴ Indivior’s veiled threats of litigation, therefore, are empty.

In sum, there is ample statutory and regulatory support for FDA to determine that Subutex’s ODD expired in 2009. More to the point, FDA’s failure to do so would violate the Orphan Drug Act.

³³ See GA Memorandum, p. 2 (Exhibit 4).

³⁴ See *Eagle Pharmas, Inc. v. Azar*, Civ. Action No. 16-790 (D.D.C. June 8, 2018); *Depomed, Inc. v. HHS*, 66 F. Supp. 3d 217, 229 (D.D.C. 2014).

III. Subutex Was Not Eligible for ODD in 1994

Although Indivior spends little time addressing Braeburn's statutory and regulatory arguments, it goes to great lengths to defend the validity of the 1994 decision to grant ODD to Subutex. But its assertions regarding the facts and circumstances surrounding its 1993 ODD submission, and FDA's 1994 ODD decision, are no more accurate or persuasive than its already debunked claims regarding the Nutropin Depot and Tyvaso examples. The bottom line is that, despite its best efforts, Indivior cannot hide the fact that the "estimates and justifications" it provided to FDA for cost recovery purposes in 1993 were very different than the estimates and predictions it was relying upon to run its business *at the very same time*.

Indivior initially alleges that Braeburn simply is confused about the timeline. According to Indivior, the company's belief that it would be possible to transition buprenorphine into the mainstream practice of medicine only crystallized in 1995 after issuance of an Institute of Medicine ("IOM") report. Ind., at 18-21. Thus, Indivior's contrary assertions in its 1993 ODD request purportedly were not false or misleading, but instead reflected Indivior's "reasonably and sincerely" held beliefs at that time. Ind., at 2.

But Indivior's proposed timeline, once again, is based upon a single, cherry-picked sentence that ignores the full context of the timeline recounted by Charles O'Keeffe, Executive Vice President of Indivior's pharmaceutical business at the time, in his 2003 article describing the history of Indivior's development of buprenorphine. Elsewhere in that article, Mr. O'Keeffe stated that it "seemed possible that ... buprenorphine might be exempted from some of the burdens associated with the use of methadone and LAAM."³⁵ This reference is tied to events occurring as early as 1992 – at least a year *before* submission of Indivior's revised ODD request – and without reference to the purportedly critical IOM report. Indivior, of course, overlooks it.

In addition, Indivior's timeline fails to account for the fact that the company's legislative plan was "inextricably intertwined" with its "effort to develop and win approval" of Subutex for treatment of OUD.³⁶ In other words, when Indivior's Board of Directors approved the plan to move forward with development of Subutex, it did so only because it believed changing the law was an achievable goal. This, Indivior believed, was necessary to recover its investment in developing buprenorphine. As Charles O'Keeffe explained in 2003:

from a corporate perspective it seemed unlikely that a drug confined to a limited number of clinics that were already comfortable using generic methadone would be used enough to justify the investment involved in taking buprenorphine through the regulatory process.³⁷

³⁵ J. Jaffe, C. O'Keeffe, From morphine clinics to buprenorphine: regulating opioid agonist treatment of addiction in the United States. Drug and Alcohol Dependence. Page S7 (2003) ("O'Keeffe Article") (Braeburn CP, Exhibit 17).

³⁶ O'Keeffe Article, at S7.

³⁷ O'Keeffe Article, at S7.

The business plan thus included a legislative component that the Board presumably would not have approved if company officials did not believe it was achievable. Significantly, this Board decision appears to have been made *before* submission of the 1993 ODD request since the business plan also included a goal of seeking ODD in order to obtain ODE upon approval.³⁸ Thus, while the 1995 IOM may have strengthened Indivior's belief that buprenorphine could reach the mainstream practice of medicine, it does not appear to have been the origin of that belief.

Second, Indivior claims that its statements to FDA about the likelihood of legal changes during the life of Subutex were accurate because they focused solely on federal *regulations*, not marketplace changes generally. Ind., at 23-34. But there are two problems with this defense. First, Indivior's statement was not limited narrowly to regulations; instead, it also referred generally to the "limitation" establishing a maximum patient population for addiction treatment. This "limitation" on patient population, of course, could be modified by both regulatory and *statutory* changes (as occurred in 2000 with passage of DATA 2000).

Which leads to the second problem: if Indivior's representation was limited to federal regulations (as it contends), its statement, while perhaps not literally false, was nevertheless highly misleading. As FDA well knows, a statement can be literally true but misleading if it omits material information. This is the problem with "half-truths." Here, even if Indivior reasonably and sincerely believed that the patient population limitations were unlikely to be modified *by regulation*, it also appears to have reasonably and sincerely believed that those limitations could be modified *by statute* within five years (as evidenced by the Board of Director's approval of its business and legislative plan). Consequently, its assertion that the patient population "limitation" was unlikely to be modified *by regulation*, without more, is misleading because it omits material information about the likelihood of *statutory* changes that Indivior officials have conceded "seemed possible" at the time.

Moreover, Indivior's misleading representations were not limited simply to the size of the projected patient population: Indivior also informed FDA that pricing options would be limited "since the product will be competing in the same marketplace with methadone/LAAM."³⁹ But when buprenorphine was exempted from exclusive use in methadone clinics by DATA 2000, Subutex no longer had to compete in the same marketplace with methadone and LAAM, and Indivior was free to raise its prices substantially. This, in fact, was Indivior's plan and expectation from the beginning, although it never communicated this expectation to FDA. Because of this increased price flexibility, Indivior was able to generate significant profits from Subutex after approval in 2002. See Braeburn CP, Exh. 6. Moreover, this was so even if (as Indivior contends) the number of patients who actually used Subutex was not significantly higher than the number projected. See Ind., at 12.

Third, Indivior asserts that even if its statements to FDA were false or misleading, they were not "material" because FDA never relied upon them. Ind., at 21-23. Indivior contends that this lack of reliance is demonstrated by the numerous sensitivity analyses FDA performed when assessing its 1993 request for ODD. Ind., at 21-23. But this is beside the point. Even if FDA conducted its own sensitivity analyses, all of them explicitly relied upon Indivior's inaccurate

³⁸ O'Keeffe Article, at S8.

³⁹ Subutex ODD Request (Nov. 17, 1993) (Braeburn CP, Exh. 16).

information *as a baseline*. If Indivior had provided accurate, non-misleading information to FDA in its 1993 ODD request, the baseline for FDA’s sensitivity analyses presumably would have been higher – perhaps much higher – and the results of FDA’s decision could have been very different. After all, if one starts from a baseline of 100,000 patients, the result of a 50% increase will be much lower than if one starts from a baseline of 200,000 patients (*i.e.*, a difference of 150,000 patients).

Moreover, Indivior once again “overlooks” explicit FDA statements indicating that the Agency did, in fact, rely upon Indivior’s patient population estimates. In particular, FDA states:

The sponsor maintains that the maximum number of treatment seeking addicts that could be treated is limited to 104,000 since there are only 115,000 treatment slots for methadone[e], et al., in existing treatment facilities. ... It is reasonable to assume that there will be virtually no change in the treatment-seeking population, or that any positive shift will be incremental. *Thus, over seven years, the additional patients on this product beyond those projected by the sponsor should be inconsequential economically on the results of this analysis.*⁴⁰

This is an important passage – and one that should not be overlooked by FDA – because it clearly demonstrates the Agency’s reliance on Indivior’s inaccurate and misleading estimates regarding projected limitations on the size of the patient population during the first seven years after marketing approval.

Indivior also contends that it was not required to disclose information about its potential lobbying activities because that is not “material information” required by FDA’s regulations. Ind., at 15. FDA’s regulations, however, clearly require sponsors to submit “estimates,” “projections,” and “justifications” regarding expected revenues, market share and pricing. 21 C.F.R. § 316.21(c)(6). While “estimates” and “projections” are not facts, a regulatory requirement to provide “estimates” does not give a sponsor free rein to provide *inaccurate* estimates that omit *material information*. Yet it appears this is exactly what Indivior did by providing artificially depressed patient population and pricing estimates that failed to incorporate true and accurate projections regarding the likelihood of statutory changes during the seven-year marketing period. Thus, even if Indivior was not required to disclose lobbying plans *per se*, it was required to provide accurate estimates regarding revenue, market share and pricing that reflected those lobbying plans.

Finally, Indivior argues that FDA has no authority under the statute or FDA’s regulations to consider new information about buprenorphine’s cost recovery, such as passage of DATA 2000 or Indivior’s substantial, monopoly profits reaped over the years. Ind., at 25-26. Indivior specifically relies upon 21 U.S.C. § 360bb(a)(2), which provides that ODD determinations “shall be made on the basis of the facts and circumstances as of the date the request for designation of the drug under this subsection is made.” Indivior also seeks to distinguish the Evista example identified by Braeburn, arguing that it involved unique facts that do not apply to Sublocade. Ind., at 26-28.

⁴⁰ FDA Review of ODD Request for Subutex, p. 5 (June 14, 1994) (Braeburn CP, Exh. 4).

Indivior, however, is wrong on all counts. Neither the statute nor FDA's regulations prohibit the Agency from considering new information to support a revocation decision. On the contrary, FDA's regulations explicitly state that if the Agency "subsequently finds" that a drug was not eligible for ODD at the time of the request, FDA has ample authority to revoke ODD. 21 C.F.R. § 316.29(c). In most cases, this "subsequent finding" will, of necessity, be based upon *new information*. Moreover, the regulation is entirely consistent with 21 U.S.C. § 360bb(a)(2) because the new information simply elucidates the "facts and circumstances *as of the date of the request*" for ODD. *Id.* (emphasis added).⁴¹

Thus, while FDA may not be able to revoke ODD based solely upon changing circumstances (*i.e.*, growth in the relevant patient population beyond 200,000), the Agency retains broad discretion to revoke ODD if those changing circumstances indicate that the original decision itself was flawed. Indeed, it appears FDA did just this when it revoked ODD for a number of drugs, including papaverine, methylnaltrexone and lisinopril oral solution, based upon new information indicating that the potential target population could be significantly larger than originally assumed.⁴²

This type of new information is particularly relevant for revocation purposes when ODD is granted under the Cost Recovery Prong. In such situations, ODD is based almost entirely on *assumptions* about the future marketing and marketplace for the orphan drug. In the past, FDA has sought to ensure that these assumptions are not speculative and that they instead meet the threshold for presenting a "reasonably likely scenario."⁴³ If new information demonstrates that the drug is highly profitable, this could indicate that the original assumptions were unreasonable *at the time they were made*, which would support revocation.

Indeed, in the Evista situation, FDA imposed ongoing reporting requirements on the sponsor – extending even after approval – to substantiate the reasonableness of the Agency's original assumptions regarding cost-recovery. Although FDA did not revoke Evista's ODD, the Agency indicated that if new information obtained after approval failed to substantiate the reasonableness of its original assumptions, FDA could use the new information to revoke ODD under its regulations.⁴⁴

Indivior, however, contends that the Evista situation is inapplicable because FDA was particularly concerned about the reasonableness of the sponsors projections. Ind., at 26-28. Indivior further asserts that the Evista sponsor failed to carry its burden of demonstrating that the

⁴¹ In any event, it is unlikely that 21 U.S.C. § 360bb(a)(2) could be applied to ODD decisions based on the Cost Recovery Prong because those determinations are not based on "facts and circumstances at the time" of the ODD decision but rather estimates and predictions about future marketing conditions. This may be why FDA's revocation regulation does not limit the Agency's authority to consider future developments with respect to cost recovery decisions in the same way it does for patient population decisions. See 21 C.F.R. § 316.29(c).

⁴² Kurt Karst, FDA Law Blog, *FDA More Than Doubles the Number of Orphan Drug Designation Revocations Overnight* (May 20, 2016) (observing that the revocations appear to be based on "new information"), available at www.fdalawblog.net/2016/05/fda-more-than-doubles-the-number-of-orphan-drug-designation-revocations-overnight.

⁴³ See ODD Review for Raloxifene (Evista), p. 13 (May 20, 2005) (Braeburn CP, Exh. 8).

⁴⁴ See ODD Review for Raloxifene (Evista), pp. 13-14.

statutory standards were satisfied and thus that had to “cut a deal” with FDA to obtain ODD. Ind., at 27. That deal resulted in what Indivior describes variously as a “preliminar[y]” or “provisional designation” that was contingent on the sponsor’s agreement to provide additional information during development and after approval. Ind., at 27. For all of these reasons, Indivior asserts that the Evista situation is unique and “provides no support for Braeburn’s position in this matter.” Ind., at 28.

Not surprisingly, there are several major defects with Indivior’s analysis. First, there is no such thing as a “provisional designation” under the statute or FDA’s regulation. It is instead an imaginary concept that Indivior seems to have created out of whole cloth. As Indivior well knows, FDA has no authority to grant ODD unless the sponsor satisfies all applicable statutory and regulatory requirements. In this case, contrary to Indivior’s contention, FDA unequivocally determined that the Evista sponsor satisfied those requirements:

After considering all the information presented in this request, it is this reviewer’s opinion that the sponsor has presented available documentation that supports their contention that there is no reasonable expectation that costs of research and development can be recovered by sales in the U.S., as required under 21 CFR 316.21(c).⁴⁵

Second, although FDA required the Evista sponsor to submit additional reports after designation (and even after approval), the Agency also explained that this action was fully authorized by its regulations.⁴⁶ Importantly, the Agency specifically stated that its revocation regulation provided it with legal authority to revoke ODD based upon such new information, including sales data obtained after approval. As FDA clarified: “At each of these time points, OOPD will need to determine if the designation and/or marketing exclusivity should remain in place or whether the designation and/or exclusivity should be revoked *as permitted under 21 CFR 316.29*.⁴⁷ Indivior fails to explain how the revocation regulations could apply more broadly to Evista than to Sublocade (even assuming for the sake of argument that there are factual differences between the two situations). FDA, of course, does not possess broader revocation authority over one situation than the other – its power to revoke ODD based on new information applies equally to both drugs. The fact that it did not impose similar ongoing disclosure requirements on Subutex as it did for Evista thus is irrelevant to the issue of whether it possesses authority to revoke ODD now based on new information demonstrating that the original assumptions presented by Indivior were unreasonable.

There is thus clear Agency precedent supporting FDA’s broad discretion to revoke ODD, particularly in the cost recovery area, whenever new information indicates that the Agency’s original assumptions were unreasonable. This is exactly the situation raised in Braeburn’s Citizen Petition. Because this new information clearly demonstrates that the assumptions underlying the original ODD request and decision were invalid and inaccurate – and thus that Subutex

⁴⁵ See ODD Review for Raloxifene (Evista), p. 13.

⁴⁶ See ODD Review for Raloxifene (Evista), p. 13.

⁴⁷ See ODD Review for Raloxifene (Evista), p. 13 (emphasis added).

(buprenorphine) was not eligible for ODD “at the time of submission of the request therefor” – FDA should revoke that ODD pursuant 21 C.F.R. § 316.29.

IV. BRIXADI Weekly Is Not Viable Clinically or Commercially As a Stand-Alone Product

In its comments, Indivior offers to selectively waive ODE to permit FDA to immediately approve the weekly version of BRIXADI™ (buprenorphine) Extended-Release Injection, but not the monthly version of BRIXADI. As Indivior surely knows, this is an empty gesture because weekly BRIXADI would not be clinically or commercially viable as a standalone product.⁴⁸ ***Therefore, neither FDA nor anybody else should be under any illusions: Braeburn cannot and will not seek approval of or commercially market BRIXADI Weekly as a standalone product.*** If FDA decides to block approval of BRIXADI Monthly, it will, as a practical matter, also be blocking patient access to BRIXADI Weekly.

BRIXADI was studied and is intended for use as an *integrated system* involving both once-weekly and once-monthly presentations. For example, BRIXADI’s labeling provides detailed instructions for patients to transition directly from weekly to monthly dosing, and back again, based on clinical judgment and using an “oral-to-depot-to-oral” equivalent dose. In this way, the BRIXADI weekly and monthly presentations function as an integrated system designed to avoid the need for an initial titration period with oral buprenorphine. For this reason (and with FDA’s agreement), BRIXADI was studied in the pivotal clinical trial as an integrated system, not as standalone weekly and monthly injections. The primary efficacy analysis was conducted only at the end of 12 weeks of Weekly BRIXADI AND 12 weeks of Monthly BRIXADI. In short, Braeburn has no clinical endpoint data for BRIXADI Weekly. Consequently (and as Indivior well knows), this would put Braeburn in the position of commercializing and educating healthcare professionals *absent basic efficacy data* on BRIXADI Weekly, which is essential to underpin clinical judgment and treatment decision-making. For this reason alone, it is patently obvious BRIXADI Weekly is not commercially or clinically viable.

Even if FDA would be willing to approve the weekly version of BRIXADI as a standalone in the absence of clinical endpoint data, such approval would create the potential for medication errors and other unanticipated, possibly serious, safety issues. Most importantly, BRIXADI Monthly and Sublocade are not interchangeable. Each product offers different doses, substantially different pharmacokinetic profiles and was clinically studied in very different ways.

Nevertheless, it is expected that patients on weekly BRIXADI will eventually convert to a monthly depot formulation as part of a physician-guided treatment regimen. Without the availability of monthly BRIXADI, the only conversion alternative will be Sublocade. However, there are no adequate instructions or data for transitioning patients from BRIXADI Weekly to Sublocade. For example, physicians will not know whether to use the required Sublocade loading dose for patients transitioning from weekly Brixadi, with the potential to dramatically increase buprenorphine exposure in patients who are otherwise established to be clinically stable. Dosing errors may also lead to lack of efficacy and/or subsequent risk of overdose or, conversely (and

⁴⁸ It is an empty gesture for the independent reason that Sublocade does not have ODE and, for the reasons set forth in Braeburn’s petition (and otherwise), is not eligible for ODE.

more likely), overmedication. If a healthcare professional were to request guidance from either sponsor on how to transition a patient on BRIXADI Weekly to Sublocade, both Indivior and Braeburn would be prohibited from providing any such guidance as this dosing combination has never been studied. Moreover, it is unknown whether Sublocade can be safely administered in the same injection site of a previous BRIXADI injection and, at a minimum, what such a rotation schedule would look like. Thus, the use of Sublocade following treatment with weekly BRIXADI not only would be considered off-label, but also may lead to medication errors that could be potentially fatal.

It is stating the obvious, but these considerations are some of the factors that would make weekly BRIXADI clinically and commercial unsupportable as a standalone product. For all of these reasons, Indivior's offer is a sham and generally intended to distract from the indisputable fact that Sublocade is not a *bona fide* orphan drug for which ODD, or ODE, is supportable. FDA thus should give no weight to this specious ploy.⁴⁹

V. Conclusion

For the reasons discussed above, Sublocade is not now and never has been eligible for ODD. Accordingly, FDA should use its authority to revoke Sublocade's ODD pursuant to 21 C.F.R. § 316.29(a) and, concomitantly, refuse to grant, or revoke, ODE under that same regulation. These actions will protect the integrity of the Orphan Drug Act by rejecting transparent evergreening tactics for products that do not qualify as *bona fide* orphan drugs. More importantly, they will maintain robust incentives for companies to invest in new and innovative treatment options for OUD patients to combat the ongoing opioid crisis.

Thank you for your consideration of these comments, and please do not hesitate to contact me directly if you have any questions.

Sincerely,



Scott M. Lassman
Counsel to Braeburn, Inc.

cc: Dr. Janet Maynard, Director, Office of Orphan Product Development
Elizabeth Dickinson, Office of Chief Counsel
Sharon Hertz, M.D., Director, DAAAP

⁴⁹ Indivior also argues that Sublocade is entitled to ODE because the FDARA clinical superiority requirement is inapplicable and, even if it does apply, Sublocade is clinically superior to previously approved buprenorphine products. Ind., at 29-34. While Braeburn disagrees with these positions, it declines to address them here since they are outside the scope of Braeburn's Citizen Petition, which focused exclusively on revocation of ODD pursuant to 21 C.F.R. § 316.29 and the effects of such revocation on ODE. Braeburn specifically reserved its right to address "clinical superiority" in a separate submission, which it has done. Therefore, Indivior's request for "alternative or different administrative action" regarding "clinical superiority" must be made, if at all, in a separate Citizen Petition. 21 C.F.R. § 10.30(d).

EXHIBIT 1

[FDA Home³](#)[Developing Products for Rare Diseases & Conditions⁴](#)

Search Orphan Drug Designations and Approvals

Generic Name:	Somatropin
Trade Name:	Nutropin
Date Designated:	03/06/1987
Orphan Designation:	For use in the long-term treatment of children who have growth failure due to a lack of adequate endogenous growth hormone secretion.
Orphan Designation Status:	Designated/Approved
Marketing Approval Date:	10/17/1985
Approved Labeled Indication:	
Exclusivity End Date:	10/17/1992
Sponsor:	Genentech, Inc. 1 DNA Way South San Francisco, California 94080 USA

The sponsor address listed is the last reported by the sponsor to OOPD.

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Search Orphan Drug Designations and Approvals

Generic Name:	Somatropin (rDNA origin)
Trade Name:	Nutropin Depot
Date Designated:	10/28/1999
Orphan Designation:	Long-term treatment of children who have growth failure due to a lack of adequate endogenous growth hormone secretion.
Orphan Designation Status:	Designated/Approved
Marketing Approval Date:	12/22/1999
Approved Labeled Indication:	Long-term treatment of growth failure due to a lack of adequate endogenous growth hormone secretion for once- or twice-a-month administration.
Exclusivity End Date:	N/A
Sponsor:	Genentech, Inc. 1 DNA Way South San Francisco, California 94080 USA

The sponsor address listed is the last reported by the sponsor to OOPD.

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EXHIBIT 2

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1/1-3621



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P.O. Box 14186
55 T.W. Alexander Drive
Research Triangle Park, NC 27709
tel 919.485.8350
fax 919.485.8352

DEC 15 2011

FILE COPY

14 December 2011

OFFICE OF ORPHAN
PRODUCTS DEVELOPMENT

Gayatri Rao, M.D., J.D., Acting Director
Office of Orphan Products Development (OOPD)
Food and Drug Administration
WO32-5271
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: Request for orphan designation for oral treprostinil diethanolamine (UT-15C)

Dear Dr. Rao:

Please find attached a request for orphan designation for oral treprostinil diethanolamine (UT-15C) for the treatment of Pulmonary Arterial Hypertension ("PAH"), a well-recognized rare condition. We are submitting one original and one photocopy, for your review. United Therapeutics' anticipates submitting a New Drug Application for treprostinil diethanolamine by the end of 2011.

Should you have any questions, please contact Rex Mauthe, M.S, Senior Director Regulatory Affairs by email at rmauthe@unither.com or by phone at 919-425-8127.

Sincerely,

A handwritten signature in black ink, appearing to read "Dean Bunce".

Dean Bunce, RAC
EVP Regulatory Affairs and Compliance
United Therapeutics Corp.

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DEC 15 2011

OFFICE OF ORPHAN
PRODUCTS DEVELOPMENT

Request for Orphan Designation

Treprostinil Diethanolamine (UT-15C) for the
Treatment of Pulmonary Arterial Hypertension

United Therapeutics Corporation
55 TW Alexander Drive
Research Triangle Park, NC 27709

14 December 2011

14 December 2011

FDA 0002

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(1) Statement Requesting Orphan Drug Designation

United Therapeutics is requesting orphan drug designation for UT-15C (treprostинil diethanolamine) for the treatment of pulmonary arterial hypertension.

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(2) Name and Address of Sponsor

United Therapeutics Corporation
55 TW Alexander Drive
PO Box 14186
Research Triangle Park, NC 27709

Contact:

Rex Mauthe, MBA
Senior Director, Regulatory Affairs
Tel no. 919-485-8350
Fax no. 919-313-1298
rmauthe@unither.com

Drug name:

Active Pharmaceutical Ingredient: Treprostinil diethanolamine
United Therapeutics Code Name: UT-15C

~~CONFIDENTIAL~~**United Therapeutics Corporation**~~CONFIDENTIAL~~**(3) Description of the Rare Disease**

Pulmonary arterial hypertension (PAH), defined as an elevation in pulmonary arterial pressure and pulmonary vascular resistance, is a severe hemodynamic abnormality common to a variety of diseases and syndromes. Elevation in pulmonary arterial pressure causes an increase in right ventricular afterload, impairing right ventricular function and ultimately leading to heart failure and death.

The typical etiologies of PAH include idiopathic, heritable or PAH associated with collagen vascular / connective tissue disease, portal hypertension, infection with the human immunodeficiency virus (HIV), a history of cocaine inhalation and a history of appetite suppressant use (Simonneau, 2009). An estimated annual incidence of approximately two cases per million has been reported for idiopathic PAH (Rich, 1987; Rubin, 1997). The familial or heritable form of PAH accounts for approximately 6% of all cases of PAH; however, this may be an underestimate as familial PAH is histologically indistinguishable from idiopathic PAH (Farber, 2004). There are twice as many female as male patients. Although it can present at any age, the mean age at diagnosis is 36 years with a mean time from the onset of symptoms to diagnosis of two years (Gaine, 1998).

In view of the fact that the symptoms and signs of PAH are non-specific, the diagnosis is often delayed and is ultimately confirmed by invasive hemodynamic evaluation of patients by catheterization of the right heart and pulmonary artery (Chemla, 2002). The hemodynamic definition of PAH was revised to the following during the fourth World Symposium on Pulmonary Hypertension which took place in 2008 in Dana Point, California: mean pulmonary artery pressure (PAPm) at least 25 mmHg and mean pulmonary capillary wedge pressure (PCWPm) or left ventricular end-diastolic pressure (LVEDP) no more than 15 mmHg. The predominant symptoms of PAH are dyspnea (which is exacerbated on exercise), fatigue, weakness, chest pain at rest or on exertion, dizziness, syncope and hemoptysis. The clinical signs reflect pulmonary hypertension, right ventricular hypertrophy, hypoxemia and right heart dysfunction (Galie, 2009).

In the late 1960's, an increased frequency of Primary Pulmonary Hypertension was linked to the use of the appetite suppressant aminorex fumarate. This led to WHO convening the first World Symposium on Pulmonary Hypertension (PH) in Geneva in 1973. PH was classified into two categories; either primary pulmonary hypertension (PPH), defined as PH of no known cause, or secondary pulmonary hypertension (SPH), which was due to identifiable causes or risk factors (Hatano and Strasser, 1975).

This classification of PH was modified at the Second World Symposium in 1998 in Evian (Rich et al., 1998) to reflect advances in the understanding of pulmonary vascular diseases and to recognize the pathophysiological and therapeutic similarities between primary pulmonary hypertension and pulmonary hypertension co-existing with certain other disorders. These were linked together under the term "pulmonary arterial hypertension," which encompassed primary pulmonary hypertension (both sporadic and familial) and pulmonary hypertension related to the following conditions: connective

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tissue disease; congenital heart disease; portal hypertension; HIV infection; drugs/toxins (e.g. aminorex, fenfluramine, cocaine) and persistent PH of the newborn. Further, pulmonary arterial hypertension was separated from other forms of PH, namely, pulmonary venous hypertension; PH associated with disorders of the respiratory system and/or hypoxemia; PH due to chronic thrombotic and/or embolic disease and PH due to disorders directly affecting the pulmonary vasculature. The term secondary pulmonary hypertension was abandoned.

In addition, the Evian meeting emphasized the role of functional assessment of PH patients. A functional classification, modified from the New York Heart Association Classification was agreed - The WHO Functional Assessment Classification.

Shortcomings in the Evian classification however, became clear with its application in the clinical setting. This clinical classification of PH was thus modified further at Venice in 2003 where the term Primary PAH was abandoned in favor of idiopathic PAH (IPAH), or, when supported by genetic evidence, familial PAH (FPAH). Other modifications include the reclassification of pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis as part of, "PAH associated with significant venous or capillary involvement" and an update of risk factors for PH (Simonneau et al., 2004).

More recently at the fourth World Symposium in 2008, the classification of PH was again modified; however, the general structure of the classification was maintained (Simonneau et al., 2009). The majority of the modifications concerned Group 1 (PAH) in order to make it more homogenous. The current classification of PAH within PH is as follows:

Group 1: Pulmonary arterial hypertension (PAH)

- 1.1 Idiopathic PAH
- 1.2 Heritable (formerly familial)
 - 1.2.1 BMPR2
 - 1.2.2 ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)
 - 1.2.3 Unknown
- 1.3 Drug- and toxin-induced
- 1.4 Associated with
 - 1.4.1 Connective tissue diseases
 - 1.4.2 HIV infection
 - 1.4.3 Portal hypertension
 - 1.4.4 Congenital heart diseases
 - 1.4.5 Schistosomiasis
 - 1.4.6 Chronic hemolytic anemia
- 1.5 Persistent pulmonary hypertension of the newborn

The therapeutic goals for the clinical management of patients with PAH include: vasodilatation of the pulmonary arteries to reduce pulmonary vascular resistance and thereby reduce afterload on the right ventricle; management of fluid retention due to right ventricular dysfunction; support of myocardial performance; and prevention of in-situ pulmonary arterial thrombosis. These measures are all intended to improve the patients'

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functional capacity, with an endpoint measuring exercise capacity, enhance their quality of life and prolong survival (Gildea, 2003).

Current therapeutic options include anticoagulants (e.g., warfarin), calcium channel blockers (e.g., nifedipine), endothelin receptor antagonists (ERAs; e.g., bosentan, ambrisentan), phosphodiesterase-5 inhibitors (PDE5-Is; e.g., sildenafil, tadalafil), other vasodilators (e.g., nitric oxide) and prostacyclin analogues (e.g., epoprostenol, iloprost, treprostинil). In addition, patients may require other supportive therapies such as digoxin, diuretics and supplemental oxygen. Invasive medical interventions to treat more advanced disease include balloon atrial septostomy and ultimately heart-lung transplantation. Unfortunately, not all patients benefit from these therapies or their benefit is limited. Treprostинil diethanolamine, delivered as an orally bioavailable prostacyclin, is expected to provide additional benefits and therapeutics options to these patients.

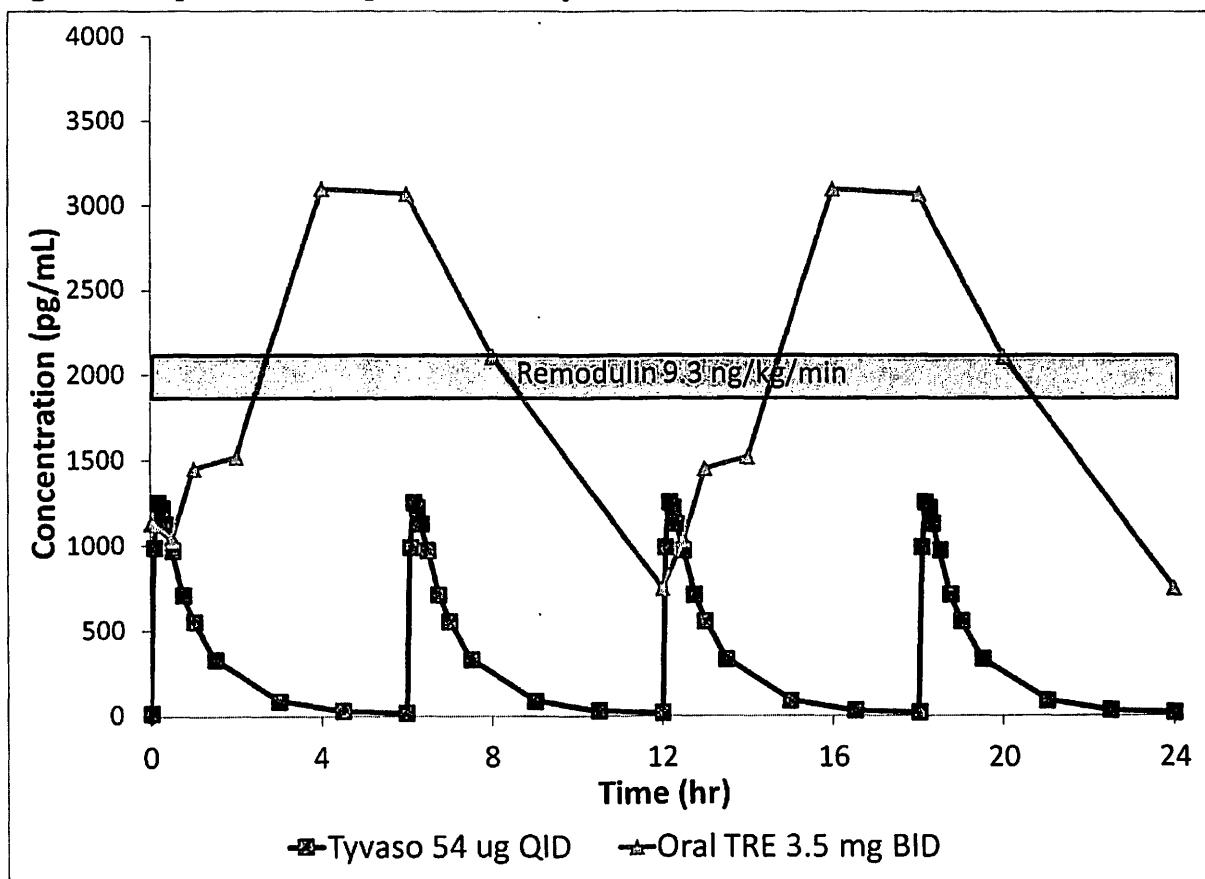
The proposed indication is:

Treatment of pulmonary arterial hypertension (WHO Group 1) to improve exercise capacity.

~~CONFIDENTIAL~~**United Therapeutics Corporation****CONFIDENTIAL****(4) Description of the Drug and Scientific Rationale**

Intravenous prostacyclin therapy has been shown to prolong survival in patients with PAH (Barst, 1996) and is considered by many providers as the “gold standard” of care for the treatment of PAH. Parenteral prostacyclins are typically used later in the course of disease due to the risks and difficulties associated with the infusion process. A synthetic salt of prostacyclin (Flolan[®]) was developed and has demonstrated the clinical utility of prostacyclin in the treatment of pulmonary hypertension and other vascular diseases. Unfortunately, due to its very short half-life and chemical instability, Flolan must be continuously infused by intravenous (IV) delivery. Various analogs have been developed that have overcome some of these limitations, but the few orally active prostacyclins have remained limited by their short half-life and poor solubility. Treprostinil is a chemically stable, longer acting prostacyclin analog that has shown clinical effectiveness when administered by the continuous subcutaneous route (Remodulin[®]), the continuous intravenous route (Remodulin), and the inhaled route by intermittent nebulization (Tyvaso[®]).

Remodulin[®] (treprostinil) Injection and Tyvaso[®] (treprostinil) Inhalation Solution are approved for the treatment of patients with PAH. The active pharmaceutical ingredient of these products is treprostinil (sodium), a stable prostacyclin analogue with an extended half-life, compared to epoprostenol. While Remodulin and Tyvaso have provided significant benefit to patients with this rare, life-threatening disease, the rigors of continuous parenteral infusion and intermittent inhalation therapy via infusion pump and nebulizer devices, respectively, can be burdensome to patients. Accordingly, United Therapeutics developed an oral sustained-release formulation of treprostinil, treprostinil diethanolamine (UT-15C), as an alternative dosage form to deliver the benefits of treprostinil therapy to PAH patients more conveniently and without the complexity of parenteral or inhaled delivery devices and which is therefore clinically superior to the other routes of treprostinil administration. Oral administration of UT-15C results in systemic exposure to treprostinil that is similar to that achieved with efficacious doses of Remodulin, as demonstrated in Figure 1 (data from the Remodulin and Tyvaso package inserts, 2011), without the potential serious consequences associated with parenteral therapy including risks of catheter-related blood stream infection with intravenous infusion and intolerable infusion site pain with subcutaneous delivery.

~~CONFIDENTIAL~~**United Therapeutics Corporation**~~CONFIDENTIAL~~**Figure 1 Treprostinil Comparative Steady-State Pharmacokinetics in PAH Patients**

Treprostinil diethanolamine was selected from a series of other salts based on critical physicochemical characteristics which were predicted to improve the bioavailability and allow the pharmaceutical development of an orally active formulation that could be delivered as a sustained release dosage form. The formulation utilizes osmotic tablet technology, a proven approach that provides a more uniform and controlled drug release profile. The formulation releases treprostinil over approximately 12 hours, thus allowing for a twice daily dosing regimen. This is compared to treprostinil delivered parenterally which is administered by continuous infusion with an approximately 4 hour half-life.

UT-15C is currently being studied as a sustained release (SR) oral tablet formulation and completed studies demonstrate that it retains the bioactivity of the marketed, parenteral treprostinil sodium products (Remodulin) with an improved safety profile and more convenient dosing.

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General Pharmacology

Treprostinil, [(1R,2R,3aS,9aS) 2,3,3a,4,9,9a hexahydro 2 hydroxy 1 [(3S) 3 hydroxyoctyl] 1H benz [f]inden 5 yl]oxy]acetic acid, is a chemically stable tricyclic analogue of prostacyclin (PGI2).

The pharmacology of treprostinil has been extensively characterized in well established models that confirm the suitability of the drug for the treatment of PAH when administered by the subcutaneous, intravenous, inhaled (all as treprostinil sodium) or oral (as treprostinil diethanolamine) routes of administration.

The major pharmacological actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation. In vitro, treprostinil induced concentration dependent relaxation of rabbit isolated precontracted mesenteric arteries, inhibited adenosine diphosphate (ADP)-induced aggregation in human platelet rich plasma and inhibited ADP-induced platelet aggregation in rat platelet rich plasma. In animals, the vasodilatory effects of treprostinil reduce right and left ventricular afterload, and increase cardiac output and stroke volume. Prostacyclins lower pulmonary artery pressure, increase cardiac output without affecting the heart rate, improve systemic oxygen transport and may reverse pulmonary artery remodeling via their inhibitory effects on pulmonary artery smooth muscle cell proliferation. Increasing evidence suggests that this inhibitory effect on pulmonary artery smooth muscle cell proliferation, along with the vasodilatation and inhibition of platelet aggregation, may contribute to the therapeutic effects of prostacyclins in the treatment of pulmonary arterial hypertension. The mechanism of action is therefore likely to be multifactorial.

Treprostinil diethanolamine is an innovative salt form of treprostinil that has favorable physical characteristics for a solid dose compound. In the plasma at physiological pH, treprostinil exists in the ionized state. A rat blood pressure model study confirmed that the diethanolamine salt of treprostinil exhibits dose dependent pharmacological activity with a cardiovascular profile comparable to that of treprostinil. The hemodynamic effects of six metabolites identified from human pharmacokinetic studies have also been evaluated in the same rat model. Overall, no highly active metabolite has been identified, as all the metabolites evaluated had significantly reduced activity compared to treprostinil. Thus, it would appear that the observed pharmacological profile of UT-15C reflects the activity of the parent molecule, treprostinil, and that the contribution to that profile of any known metabolite formed in vivo would be minimal.

General Toxicology

Since the bioactive form (treprostinil) present in the bloodstream is identical following administration of treprostinil diethanolamine or treprostinil sodium (Remodulin or Tyvaso), the extensive toxicology data collected with Remodulin can also be used to support the development and safety of UT-15C. During the development of Remodulin, treprostinil sodium was administered (subcutaneously

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and / or intravenously) in safety pharmacology studies, acute toxicity studies, repeat-dose toxicity studies, reproductive toxicity studies, and genotoxicity studies.

Treprostinil sodium was administered via continuous infusion to both rats and dogs in toxicity studies for up to 6-months, which supported the chronic administration of Remodulin to patients.

In addition to the extensive toxicology data with treprostinil sodium, the toxicity and toxicokinetic profiles of UT-15C have been evaluated in acute and repeat-dose oral toxicity studies of up to 13 weeks in duration in rodents and up to 9 months duration in dogs. UT-15C has also been evaluated in safety pharmacology studies, the complete ICH-compliant battery of reproductive-developmental toxicity studies in pregnant rats and rabbits and the potential for genotoxicity was evaluated in an oral rat micronucleus assay.

A summary of the safety pharmacology program for UT 15C is provided in Table 1. A summary of the toxicology program for UT 15C is provided in Table 2. All pivotal nonclinical studies were conducted in compliance with GLP regulations as set forth in the Title 21 of the U.S. Code of Federal Regulations, Part 58.

Table 1: UT-15C Safety Pharmacology Program

Type of Study	Species	Route of Administration	Study Number
Safety Pharmacology			
Autonomic Nervous System	Rat	oral	0200RU16.001
Respiratory	Guinea Pig	iv	1082GU16.001
Respiratory	Rat	oral	1275RU16.001
Gastrointestinal	Mice	oral	0239MU16.001
Cardiovascular- <i>in vitro</i>	HEK cells	<i>In vitro</i>	110106.DMK
Cardiovascular- <i>in vitro</i>	HEK cells	<i>In vitro</i> ^a	110204.DMK
Cardiovascular	Dog	oral	1259DU16.002
Cardiovascular	Dog	oral ^c	1259DU16.00

iv = intravenous

^a Test article was Diethanolamine

~~CONFIDENTIAL~~**United Therapeutics Corporation**~~CONFIDENTIAL~~**Table 2: UT-15C Toxicology Program**

Study Type and Duration	Route of Administration	Species	Study Number
Single-dose toxicity	oral	rat	7049-111
Single-dose toxicity	oral	dog	7049-109
Single-dose toxicity	oral	dog	7049-113
Single-dose toxicity	oral	dog	0433DU16.001
<i>Repeat-dose toxicity</i>			
5-day	oral	mouse	TPU00007
28-day	oral	mouse	AC23ZN.2G3R.BTL
13-week	oral	mouse	TPU00006
3-day	oral	rat	7049-111
14-day	oral	rat	7049-112
28-day	oral	rat	TPU00015
13-week	oral	rat	TPU00004
13-week	oral	rat	TPU00016
3-day	oral	dog	7049-109
14-day	oral	dog	7049-110
14-day	oral	dog	7049-113
13-week	oral	dog	TPU00005
9-month	oral	dog	TPU00009
<i>Genotoxicity</i>			
	<i>In vitro</i> ^a	Ames test	AA20YG.502.BTL
	<i>In vitro</i> ^a	mouse TK ^{+/−} lymphoma	19159-0-431ICH
	oral	rat micronucleus	AB18RN.125.BTL
<i>Reproductive Toxicity</i>			
Seg I	oral	rat	7049-130
Seg II range-finding	oral	rat	7049-118
Seg II	oral	rat	7049-120
Seg II range finding	oral	rabbit	7049-119
Seg II	oral	rabbit	7049-121
Seg III	oral	rat	7049-131

a. *In vitro* assays were conducted with treprostinil, the free acid of UT-15C

UT-15C administered orally to rats, mice, and dogs was generally well tolerated and dose limiting adverse effects in these species were more commonly related to GI toxicity that was characterized by vomiting (dogs only), fecal abnormalities such as few feces/soft or nonformed stools/diarrhea, intussusception (dogs only), distended GI tract and microscopic changes in the stomach and intestines. Many of these findings have been seen previously during development of Remodulin and are consistent with prostacyclin induced effects. In addition, there were no treatment-related effects on ophthalmology exams in rats and dogs, and no abnormalities on ECG evaluation or

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blood pressure in dogs.

UT-15C and treprostinil were not mutagenic or clastogenic in genotoxicity studies.

UT-15C also was not teratogenic and did not adversely affect reproductive performance, fertility or embryo/fetal viability in Segment I and Segment II fertility and embryo/fetal development studies in rats. Protocols for long-term studies in rats and mice to evaluate the carcinogenic potential of UT-15C have been reviewed by the FDA Carcinogenicity Assessment Committee, and studies are currently being conducted.

In conclusion, based on the results of the nonclinical safety pharmacology and toxicology studies, it is considered that UT-15C has an acceptable safety profile and that there are no findings that preclude long-term oral administration to humans.

Clinical Pharmacology

UT-15C (treprostinil diethanolamine) has been administered to over 1600 subjects in Phase 1-3 clinical trials. UT-15C doses of up to 3 mg twice daily (BID) have been administered to healthy volunteers, and patients with PAH have received up to 21 mg BID in the Phase 3 studies. The longest exposure is now greater than four years.

Bioavailability of an oral treprostinil diethanolamine solution up to 2 mg ranged from 21 to 25% compared to historical intravenous Remodulin® (treprostinil) Injection data. Following oral administration, treprostinil diethanolamine is widely distributed. Treprostinil diethanolamine is approximately 96% protein bound with no effect of warfarin or digoxin displacement. Pharmacokinetic data (area under the curve; AUC) indicate that Day 1 pharmacokinetic data are predictive of Day 13 and linearity was observed in plasma exposure comparing 1 mg and 2 mg doses in healthy volunteers. Food, particularly a high fat, high calorie meal, has been observed to increase absorption and prolong the exposure, contributing to the desired pharmacokinetic profile. Consistent with in vitro studies, clinical studies assessing the impact of induction and inhibition of the cytochrome P450 (CYP) 2C8 and CYP 2C9 metabolic pathways on treprostinil diethanolamine indicate CYP 2C8 appears to be of major importance and CYP 2C9 of minor importance in UT-15C SR metabolism in humans.

A comprehensive description of UT-15C (treprostinil diethanolamine), including the pharmacology, toxicology, and clinical studies completed to date may be found in the most recent Investigators' Brochure (UT-15C (treprostinil diethanolamine) Investigators' Brochure).

Clinical Efficacy and Safety

Three controlled clinical studies have been performed with UT-15C to demonstrate the clinical effectiveness in patients with PAH. The clinical development program

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was focused on two clinical populations. One pathway was centered on the investigation of UT-15C used as front-line therapy (TDE-PH-302), while the second development pathway was focused on the use of UT-15C as an add-on therapy to other approved oral therapies, specifically for patients already receiving treatment with an oral PDE5-I, ERA, or the combination of both a PDE5-I and an ERA (TDE-PH-301 and TDE-PH-308).

The clinical development UT-15C for PAH also consisted of twenty Phase 1 studies (TDE-PH-101-116, 120-123) and one Phase 2 study (TDE-PH-201). In addition, three substudies (TDE-PH-305, TDE-PH-306, and TDE-PH-307) occurred as a part of the Phase 3 program. Currently, one open label extension study (TDE-PH-304) and two additional Phase 2 studies (TDE-PH-202, TDE-PH-203) are ongoing.

Clinical Studies

Studies described in Table 3 have been completed and will be submitted in support of the regulatory application for UT-15C for PAH.

Table 3 Overview of Completed Studies with UT-15C

Protocol Number	Study Description	Sample Size	Dose of UT-15C	Duration of Dosing
TDE-PH-101	Open-label, dose escalation, pharmacokinetic and safety study with UT-15C oral solution	24	0.05, 0.125, 0.25, or 0.5 mg	Every 2 hours x 4 doses
TDE-PH-102	Open-label, two period cross-over, pharmacokinetic and safety study with single doses of UT-15C administered as SR tablets and capsules in the fasted and fed states (8-hour formulations)	28	1 mg	2 separate doses separated by a washout period
TDE-PH-103	Open-label, two period, cross-over, pharmacokinetic and safety study with single doses of UT-15C SR administered as three tablet prototypes (12-hour formulations) in the fasted and fed states	30	1 mg	3 separate doses separated by washout periods
TDE-PH-104	Open-label, randomized, double blind, placebo controlled, parallel group, pharmacokinetic and safety study with UT-15C SR administered over 13 days in escalating doses	36	1 mg BID – 3 mg BID	13 days
TDE-PH-105	Open-label, randomized, three period, three sequence, cross-over study to evaluate the effect of bosentan on steady state UT-15C SR pharmacokinetics	24	1 mg	4.5 days of dosing with and without bosentan
TDE-PH-106	Open-label, randomized, three period, three sequence, cross-over study to evaluate the effect of sildenafil on steady state UT-15C SR pharmacokinetics	18	1 mg	4.5 days of dosing with and without sildenafil

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Protocol Number	Study Description	Sample Size	Dose of UT-15C	Duration of Dosing
TDE-PH-107	Open-label, mass balance, metabolite profiling and safety study of [¹⁴ C],[³ H]UT-15C (treprostinil diethanolamine)	8	0.5 mg	1 dose
TDE-PH-108	Open-label, cross-over study to evaluate the bioavailability of a 1 mg dose of UT-15C SR administered as a single 1 mg tablet or two 0.5 mg tablets	20	1 mg	2 separate doses as 2, 0.5 mg tablets or 1, 1 mg
TDE-PH-109	Open-label, randomized, single sequence, cross-over study to evaluate the effect of repeated rifampin dosing on a single dose of UT-15C SR	20	1 mg	2 separate doses separated by a washout
TDE-PH-110	Open-label, randomized, two-period, two-sequence, cross-over study to evaluate the effect of repeated gemfibrozil or fluconazole dosing on the pharmacokinetics of a single dose of UT-15C SR	40	1 mg	2 cohorts each receiving 2 separate doses separated by a washout
TDE-PH-111	Open-label, cross-over study to evaluate the bioavailability of a 1 mg dose of UT-15C SR administered as a single 1 mg tablet or four 0.25 mg tablets	24	1 mg	2 separate doses as 4, 0.25 mg tablets or 1, 1 mg, separated by a washout
TDE-PH-112	Open-label, single-dose, pharmacokinetic and safety study in three cohorts of subjects with various degrees of hepatic impairment and one cohort of healthy volunteers	30	1 mg	1 dose in 4 cohorts
TDE-PH-113	Open-label, two-sequence, cross-over study to evaluate the bioavailability of a 1 mg dose of UT-15C as compared to a 2.5 mg dose of UT-15C SR	28	1 mg and 2.5 mg	2 separate doses separated by a washout
TDE-PH-114	Open-label, two-sequence, cross-over study to evaluate the absolute bioavailability of a 1 mg dose of UT-15C SR as compared to an IV infusion of treprostinil sodium	24	1 mg and 0.2 mg Remodulin	2 separate doses separated by a washout
TDE-PH-115	Open-label, randomized, single-dose, four-period, cross-over pharmacokinetic and safety study evaluating the effect of different meal compositions on treprostinil pharmacokinetics	32	1 mg	4 separate doses separated by washouts

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Protocol Number	Study Description	Sample Size	Dose of UT-15C	Duration of Dosing
TDE-PH-116	Open-label, single sequence, cross-over study to evaluate the effect of repeated esomeprazole dosing on the pharmacokinetics of a single dose of UT-15C SR	30	1 mg	2 separate doses separated by a washout
TDE-PH-120	Open label, single-dose, pharmacokinetic, safety and tolerability study in healthy volunteers and patients with ESRD (Two-period, two-way cross-over for those subjects with ESRD)	16	1 mg	ESRD – 2 separate doses separated by a washout; healthy volunteers – 1 dose
TDE-PH-121	Open-label, two sequence, cross-over study to evaluate the comparative bioavailability of a 1 mg dose of UT-15C SR manufactured by two independent facilities	64	1 mg	2 separate doses separated by a washout
TDE-PH-122	Open-label study to evaluate the comparative pharmacokinetics of a 0.5, 1 and 2.5 mg dose of UT-15C SR	36	0.5, 1, and 2.5 mg	3 separate doses separated by washouts
TDE-PH-123	Open-label, two-sequence, cross-over study to evaluate the comparative bioavailability of a 1 mg dose of UT-15C administered as a single UT-15C SR tablet or as a UT-15C oral solution	24	1 mg and 0.25 mg q2 hrs x 4 doses	2 doses separated by a washout
TDE-DU-101 (under IND#103,070)	Open-label, two-part, PK study in two cohorts of patients with systemic sclerosis.	28	1-4 mg BID	Up to 8 weeks
TDE-DU-201 (under IND#103,070)	Randomized, multi-center, placebo-controlled study in subjects with digital ulcers	148	0.25 mg BID starting dose with dose increasing over time	20 weeks
TDE-PH-201	Open-label, multi-center, four-cohort study in subjects with PAH	8	1 or 2 mg single dose	1 day
TDE-PH-301	Randomized, multi-center, placebo-controlled study in subjects with PAH on approved background therapy	354	0.25-1 mg BID starting dose with dose increasing over time	16 weeks
TDE-PH-302	Randomized, multi-center, placebo-controlled study in subjects with PAH on NOT receiving approved background therapy	349	0.25-1 mg BID starting dose with dose increasing over time	12 weeks

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Protocol Number	Study Description	Sample Size	Dose of UT-15C	Duration of Dosing
TDE-PH-305	Hemodynamic substudy	60	0.25-1 mg BID starting dose with dose increasing over time	12 or 16 weeks (substudy of TDE-PH-301 or 302)
TDE-PH-306	Open-label pharmacokinetic, study	74	0.25-1 mg BID starting dose with dose increasing over time	1 day (substudy of TDE-PH-304)
TDE-PH-308	Randomized, multi-center, placebo-controlled study in subjects with PAH on approved background therapy	310	0.25 mg BID starting dose with dose increasing over time	16 weeks

~~CONFIDENTIAL~~**United Therapeutics Corporation**~~CONFIDENTIAL~~**(5) Clinical Superiority of UT-15C**

This designation request seeks OOPD's designation of a new sustained release oral dosage form of treprostinil for PAH (treprostinil diethanolamine). On June 4, 1997, FDA's Office of Orphan Products Development (OOPD) designated UTC's treprostinil as an orphan drug for the treatment of patients with primary pulmonary hypertension. This was amended to PAH on November 2, 1999. In May 2002, FDA approved NDA No. 021272 for subcutaneous delivery of treprostinil, marketed as Remodulin, for the treatment of PAH. In November 2004, FDA approved the intravenous use of Remodulin for this same indication under NDA No. 021272. On June 17, 2010, OOPD designated UTC's inhaled treprostinil, marketed as Tyvaso, for the treatment of patients with PAH after determining that the inhaled version is not the "same drug" as the previous approved versions of the drug, because it is "clinically superior" (greater safety). FDA granted UTC a period of orphan drug exclusivity applicable to the Tyvaso application, NDA No. 022387, approved on July 30, 2009. In accordance with FDA's orphan drug regulations, 21 C.F.R. Part 316, UTC submits the following plausible hypothesis that oral treprostinil – treprostinil diethanolamine – for PAH may be clinically superior on the basis that oral treprostinil makes a major contribution to patient care, and is therefore clinically superior to Remodulin and Tyvaso. See 21 C.F.R. § 316.3(b)(3)(iii).

In the preamble to FDA's December 1992 final orphan drug regulations, the Agency noted that the determination of whether a drug is clinically superior to another approved version of the same drug for the same condition based on a major contribution to patient care is made on a case-by-case basis, but that "a change in drug delivery systems might in some cases constitute a major contribution to patient care." 57 Fed. Reg. 62,076, 62,079 (Dec. 29, 1992). Furthermore, in the preamble to FDA's June 1991 proposed orphan drug regulations, FDA cited only one illustration of such a major contribution – "the development of an oral dosage form where the first drug was available only in a parenteral dosage form." 56 Fed. Reg. 3338, 3343 (June 29, 1991). Consistent with this position, in 1998, FDA determined that Novartis' reformulation of Sandostatin LAR (octreotide acetate) was clinically superior to a previously approved subcutaneous dosage form of Sandostatin, because with the new depot formulation "patients can be managed with one injection per month instead of sixty to ninety injections." Similarly, in 2007, FDA determined that Indevus' histrelin acetate implant drug product, Supprelin LA, was "clinically superior" to Supprelin on the basis that "a single histrelin subcutaneous implant could provide therapeutic blood levels for a period of 1 year versus 365 daily injections of Supprelin." Also in 2007, OOPD designated, and subsequently approved, Antisoma's (now Sanofi's) oral fludarabine phosphate, Oforta, on the basis that the drug provides a major contribution to patient care compared to the intravenous version of the drug. In the case of oral treprostinil, the drug provides a major contribution to patient care compared to both the parenteral and inhaled versions of the orphan drug.

Although treprostinil is a safe and effective agent given by subcutaneous, intravenous, and inhaled delivery, these routes of administration have significant

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limitations. Remodulin requires an infusion pump to continuously administer treprostinil either subcutaneously or intravenously. Continuous subcutaneous infusion via a self-inserted subcutaneous catheter, using an infusion pump designed for subcutaneous drug delivery, is the preferred mode of delivery. Intravenous delivery of Remodulin is administered by continuous infusion, via a surgically placed indwelling central venous catheter, using an infusion pump designed for intravenous drug delivery, and is used if subcutaneous infusion is not tolerated. In each case, to avoid potential interruptions in drug delivery, the patient must have immediate access to a backup infusion pump and either subcutaneous infusion sets or infusion sets.

Tyvaso requires a nebulizer for drug administration and must be administered during waking hours in four separate treatment sessions per day.

In contrast, the oral sustained-release formulation of treprostinil, which is administered only twice daily, would eliminate the device-driven limitations inherent with Remodulin and Tyvaso as well as the need for specialized patient dosing, use and, in the case of Tyvaso, cleaning of the device.

An oral tablet of treprostinil provides a simple, patient-friendly, and convenient dosing alternative to Remodulin and Tyvaso while avoiding the need for a specialized delivery device (i.e., an infusion pump for Remodulin and a nebulizer for Tyvaso) that must be transported with the patient, used carefully for dosing, and vigilantly maintained. Moreover, as a sustained-release oral tablet dosage form, treprostinil provides exposure to drug over a 12-hour period. Such sustained-release dosing itself provides several benefits over inhaled treprostinil (Tyvaso), including less frequent dosing. Thus, a sustained-release oral treprostinil tablet would have significant advantages over Remodulin and Tyvaso and would make a major contribution to PAH patient care.

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(6) Subset of Persons with the Disease

Treprostинil diethanolamine (UT-15C) is intended for the treatment of patients with pulmonary arterial hypertension.

~~CONFIDENTIAL~~**United Therapeutics Corporation****CONFIDENTIAL****(7) Summary of the Regulatory Status**

[REDACTED]

Treprostинil diethanolamine has been granted orphan status by the European Medicines Agency (EMA).

United Therapeutics expects to file a New Drug Application for treprostинil diethanolamine in late December 2011 under NDA 203496. United Therapeutics holds approved New Drug Applications for Remodulin (treprostинil) Injection [NDA 021272] and Tyvaso (treprostинil) Inhalation Solution [NDA 022387].

~~CONFIDENTIAL~~**United Therapeutics Corporation**~~CONFIDENTIAL~~**(8) Documentation of Disease Prevalence**

Pulmonary arterial hypertension (PAH) is a disease which has been previously granted Orphan status in the United States as well as in the European Union. To qualify for Orphan status in the United States, “the disease or condition for which the drug is intended affects fewer than 200,000 people in the United States or, if the drug is a vaccine, diagnostic drug, or preventative drug, the persons to whom the drug will be administered in the United States are fewer than 200,000 per year”, as specified in Section 316.21(b) in Title 21 of the Code of Federal Regulations.

According to the 2009 Expert Consensus Document on Pulmonary Hypertension, which was reported by the American College of Cardiology Task Force on Expert Consensus Documents and the American Heart Association (McLaughlin et al, 2009), the most recent and accepted data on the prevalence of PAH in the Western world is based on a French registry of 674 PAH cases. Data from this registry suggests that the current prevalence of PAH is approximately 15 per million with a low estimate of idiopathic PAH, the most common type of PAH in the registry, at 5.9 cases/million (McLaughlin et al, 2009; Humbert et al, 2006). In addition, the authors examined regional prevalence of PAH in France and observed a range in prevalence from 5 to 25 cases per million (Humbert et al, 2006).

A slightly older reference (Peacock, 2003), which is currently referred to on the www.pah-info.com website, estimated the prevalence of then-called “severe pulmonary hypertension”, defined as primary or associated with conditions including connective tissue disease, congenital heart disease, chronic pulmonary thromboembolism, HIV infection, use of an appetite suppressant, and liver disease, of about 30 to 50 cases per million. Based on the definition of severe pulmonary hypertension, it is reasonable to use this estimate when calculating the number of cases of PAH as it is currently defined.

Extrapolating these most current prevalence estimates to the United States population, an estimated 310 million people (U.S. Census Bureau, Statistical Abstract of the United States: 2011, Table 2), it is clear that the number of PAH cases in the United States is still well below the regulatory threshold of 200,000 people with a range between 1,550 to 15,500 cases.

Estimated Prevalence (Reference)	United States Population (est. 2011)	Estimated Number of Cases (People) in the United States (2011)
15 cases per million - PAH (Humbert et al, 2006)	310,000,000	4,650
5.9 cases per million – idiopathic PAH (Humbert et al, 2006)	310,000,000	1,829
5 – 25 cases per million – regional prevalence variation (Humbert et al, 2006)	310,000,000	1,550 – 7,750
30 – 50 cases per million (Peacock, 2003)	310,000,000	9,300 – 15,500

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(9) Sponsor is the Real Party

United Therapeutics is the real party for the development of treprostinil diethanolamine (UT-15C).

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UT-15C EMA Orphan Designation.

EXHIBIT 3

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December 7, 2015

RECEIVED**DEC 08 2015****COPY BY EMAIL; ORIGINAL BY FEDERAL EXPRESS****Office of Orphan
Products Development**

Gayatri R. Rao, M.D., J.D.
 Director, Office of Orphan Products Development
 Food and Drug Administration
 10903 New Hampshire Avenue
 Silver Spring, Maryland 20993

Re: Orphan Drug Designation Request No. 11-3621
Response to OOPD Letter Dated March 9, 2012

Dear Dr. Rao:

On behalf of our client, United Therapeutics Corporation (“UTC”), we submit this letter in response to the Office of Orphan Products Development’s (“OOPD’s”) March 9, 2012 letter regarding UTC’s orphan drug designation request submitted pursuant to Section 526 of the Federal Food, Drug, and Cosmetic Act (“FDC Act”) for treprostinil diolamine for the treatment of pulmonary arterial hypertension (“PAH”). In that letter, OOPD deferred judgment on granting orphan drug designation pending additional data and information regarding prevalence and clinical superiority. As you know, FDA approved UTC’s NDA 203496 for Orenitram® (treprostinil) Extended-Release Tablets, 0.125 mg, 0.25 mg, 1mg, and 2.5 mg, on December 20, 2013 for the treatment of PAH (WHO Group 1) to improve exercise capacity. FDA, however, has not yet designated Orenitram for treating PAH (WHO Group 1) nor recognized a period of orphan drug exclusivity that would otherwise expire on December 20, 2020.

Although orphan product designation and the grant of exclusivity are related considerations, and are arguably linked when the product has already received FDA approval, for purposes of this letter and for clarity in these discussions, we separate these two analyses. The scientific data and information contained in Sections I and II of this letter, in our view, responds to OOPD’s requests for information to designate Orenitram as an orphan drug for the treatment of PAH. As such, these two sections are limited to specific responses to OOPD’s [redacted] request for additional information necessary to make

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a determination of whether Orenitram should be designated an orphan drug. Section III of this letter separately considers the issue of orphan drug exclusivity for Orenitram.

I. UTC Has Demonstrated that the U.S. Prevalence of PAH is well under the Statutory Prevalence Criterion

OOPD's March 2012 letter requested additional analysis with respect to the prevalence of PAH:

[T]o provide an adequate prevalence estimate for PAH in the United States, we ask that you use the disease description classification on page 5 of your application as a starting point and provide an estimate of the prevalence for each of the situations described as PAH. The estimate should include patients of all ages, and the calculations should use the United States population estimate at the time of submission of the application of orphan drug designation (December 2011) which is 312.7 million (PopClock. US Census Bureau. <http://www.census.gov>).

We provide that analysis in this letter, and the estimates uniformly show that the prevalence of PAH is well under the threshold of 200,000 cases nationwide.

In 2013, the Clinical Classification for Pulmonary Hypertension was amended during the 5th World Symposium on pulmonary hypertension. The updates were primarily limited to Groups 1, PAH, and 5, pulmonary hypertension with unclear multifactorial mechanisms. Persistent pulmonary hypertension of the newborn ("PPHN") was removed from Group 1 because the consensus panel determined that this group carries more differences than similarities with other PAH subgroups. This group is now designated as a new Group 1" (Group 1 double prime). In addition, pulmonary hypertension associated with chronic hemolytic anemia has moved from Group 1 to Group 5 because of varying pathology, hemodynamics, and response to traditional PAH medications. The clinical classification of PAH continues to include the following subgroups: idiopathic, heritable, drug and toxin induced, and associated with connective tissue disease, HIV infection, portal hypertension, congenital heart diseases, or schistosomiasis. A comparison of the Group 1 classifications from 2008 and 2013 is provided on the following page.

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2008 WHO Group 1: Pulmonary arterial hypertension

- 1.1 Idiopathic PAH
- 1.2 Heritable
 - 1.2.1 BMPR2
 - 1.2.2 ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)
 - 1.2.3 Unknown
- 1.3 Drug- and toxin-induced
- 1.4 Associated with
 - 1.4.1 Connective tissue diseases
 - 1.4.2 HIV infection
 - 1.4.3 Portal hypertension
 - 1.4.4 Congenital heart diseases
 - 1.4.5 Schistosomiasis
 - 1.4.6 Chronic hemolytic anemia
- 1.5 Persistent pulmonary hypertension of the newborn

2013 WHO Group 1: Pulmonary arterial hypertension

- 1.1 Idiopathic PAH
- 1.2 Heritable
 - 1.2.1 BMPR2
 - 1.2.2 ALK1, ENG, SMAD9, CAV2, KCNK3
 - 1.2.3 Unknown
- 1.3 Drug- and toxin-induced
- 1.4 Associated with
 - 1.4.1 Connective tissue diseases
 - 1.4.2 HIV infection
 - 1.4.3 Portal hypertension
 - 1.4.4 Congenital heart diseases
 - 1.4.5 Schistosomiasis

No studies have evaluated the prevalence of PAH based on the revised 2013 clinical classification, and few studies have evaluated the prevalence of PAH in the United States based on the former version of the clinical classification. The lack of a fixed diagnostic code contributes to the difficulty in determining the prevalence of PAH. Kirson, et al. (2011) used administrative claims data from 1999-2007 to approximate PAH prevalence and found a rate of 109 to 451 per million persons depending on a Commercial (age < 65 years) or Medicare (age \geq 65 years) claims source, respectively. In this analysis, PAH patients were identified by a process of exclusion and met the following criteria: (1) at least two International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnoses for primary pulmonary hypertension; and (2) no claims associated with categories two through five of the 2003 and 2008 classifications. These categories included left heart disease, lung diseases, chronic thromboembolic pulmonary hypertension, or miscellaneous pulmonary hypertension diagnoses. The authors note these rates are considerably higher than previously published reports (Humbert 2006 and Peacock 2007) due the risk of misdiagnosis and the complications associated with accurately defining PAH given the lack of a specific ICD-9-CM code. In summary, given the methodology employed, the rates cited by Kirson et al. likely represent considerable overestimates of the actual prevalence in the U.S. population.

PAH prevalence data also are available from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL), an entirely U.S. study, which enrolled 2,967 patients between March 2006 and September 2007 at 54 sites in the U.S. Frost and colleagues estimated prevalence of PAH in the

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U.S. to be 12.4 and 10.6 per million persons, based on REVEAL overall (patients with PAH, age > 3 months, and PCWP ≤ 18 mmHg) and the REVEAL cohort based on criteria previously defined in a French Registry (patients with PAH, age at diagnosis ≥ 18 years, and PCWP < 15 mmHg), respectively. The authors comment: "These numbers, despite the recognition that not all patients with PAH are included in REVEAL, provide a very conservative and carefully case-ascertained baseline for future evaluations of incidence and prevalence of PAH in the United States against which future demographic studies can be compared." Frost 2011.

The U.S.-based prevalence estimates described above were used to extrapolate the number of patients with PAH based on an estimate of the U.S. population obtained from the U.S. Census Bureau's Population Clock website from December 2011 – namely 312.7 million.

Source	Age < 65 years (est. 2011)	Age ≥ 65 years (est. 2011)	All Ages (est. 2011)
U.S. Census Bureau December 2011 Population Estimates	268,671,840	44,028,160	312,700,000
Kirson et al. 2011 PAH Prevalence Age <65 years: 109 per million PAH Prevalence Age ≥ 65 years: 451 per million	29,285	19,856	49,141
Frost et al. 2011 PAH Prevalence 10.6 to 12.4 per million			3,314 – 3,877

These estimates show that the incidence of PAH is below the 200,000 cases nationwide threshold.

In order to better describe the estimated cases of WHO Group 1 PAH by disease etiology, the following data describing the estimated percentage of the subcategories of WHO Group 1 PAH from the REVEAL Registry (from Eur. Respir. Rev. March 1, 2012 vol. 21 no. 123 8-18) are described below:

PAH Etiology	REVEAL Registry
IPAH/HPAH (1.1 and 1.2)	49%
Associated PAH:	Total: 51%
Drugs and Toxins (1.3)	5%
Connective tissue disease (1.4.1)	25%
HIV (1.4.2)	2%
Portal Hypertension (1.4.3)	5%
Congenital Heart Disease (1.4.4)	10%
Schistosomiasis (1.4.5)	0%
Other	3%

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The resulting prevalence of PAH by disease etiology is described in the table below:

PAH Etiology	Prevalence Calculation Method	Est. Prevalence Age < 65 years	Est. Prevalence Age ≥ 65 years	Est. Prevalence All Ages
Total Estimated PAH Prevalence	Kirson et al. Frost et al.	29,285	19,856	49,141 3,314 – 3,877
1.1 Idiopathic and 1.2 Heritable (49%)	Kirson et al. Frost et al.	14,350	9,729	24,079 1,624 – 1,900
1.3 Drug- and toxin-induced (5%)	Kirson et al. Frost et al.	1,464	993	2,457 166 – 194
1.4 Associated with:				
1.4.1 Connective tissue diseases (25%)	Kirson et al. Frost et al.	7,321	4,964	12,285 829 – 969
1.4.2 HIV infection (2%)	Kirson et al. Frost et al.	586	397	983 66 – 78
1.4.3 Portal hypertension (5%)	Kirson et al. Frost et al.	1,464	993	2,457 166 – 194
1.4.4 Congenital heart diseases (10%)	Kirson et al. Frost et al.	2,929	1,986	4,915 331 – 388
1.4.5 Schistosomiasis (0%)	Kirson et al. Frost et al.	0	0	0 0
Other (3%)	Kirson et al. Frost et al.	879	596	1,475 99 – 116

In sum, the estimate of PAH prevalence at the time of the sponsor's initial orphan drug designation request was between 3,314 and 49,141. Thus, even the most conservative and over-inclusive estimates of PAH prevalence include a total prevalence of PAH in the United States at slightly fewer than 50,000 patients.

II. There is a Plausible Hypothesis of Clinical Superiority

As OOPD is aware, FDA regulations permit designation of "a drug that is otherwise the same drug as an already approved drug" provided that the sponsor "can present a plausible hypothesis that its drug may be clinically superior to the first drug." 21 C.F.R. § 316.20(a). There are three separate bases for demonstrating clinical superiority: greater effectiveness than the approved drug; greater safety in a substantial portion of the target population; and that the drug provides a major contribution to patient care ("MCTPC"). 21 C.F.R. § 316.3(b)(3)(i)-(iii).

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It bears noting that FDA recently reiterated that the development of improved versions of existing drugs “is achieved through *liberally granting designation* based on a plausible hypothesis of clinical superiority.” FDA Final Rule, Orphan Drug Regulations, 78 Fed. Reg. 35,117, 35,122 (June 12, 2013) (emphasis added). Indeed, OOPD has historically shown substantial flexibility with its orphan product designations, for example the Procysbi and Ryanodex designations, each of which will be discussed in more detail below.

In OOPD’s March 2012 letter, OOPD stated its view that oral treprostinil was clinically superior to IV/SC treprostinil, but questioned UTC’s plausible hypothesis of clinical superiority of oral treprostinil over inhaled treprostinil (“Tyvaso”). [REDACTED]

[REDACTED]
Below we present three separate and independent hypotheses: (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 over Tyvaso because of [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED].

A. Oral Treprostinil will have Greater Long-Term Efficacy

UTC has collated information from eleven separately published studies of subcutaneous treprostinil, intravenous treprostinil, and intravenous epoprostenol that provide patient dosing at various intervals. These data are summarized in a table provided in Appendix 1 to this letter. While variability within the data and between different studies is expected and observed, there is a clear upward trend in every case in the dose administered over time. These data show that over time, patients’ need for pharmacological intervention increases. Whether this increase in the dose necessary to achieve pharmacologic effect is due to disease progression or tolerance to the administered drug is unknown. What is known, however, is that patients, on average, taking a given dose of treprostinil (in any dosage form), or any other prostacyclin analogue such as epoprostenol, today will require ever higher doses over time.

Although a patient taking treprostinil will require greater amounts of drug, the approved dosing regimen for Tyvaso limits the amount of drug that can be delivered. Specifically, patients are limited to a maximum of nine breaths of drug in each of up to four sessions per day and the dosing instructions are to titrate up to the maximum tolerated dose, potentially reaching the maximum permitted dose three-to-six weeks after

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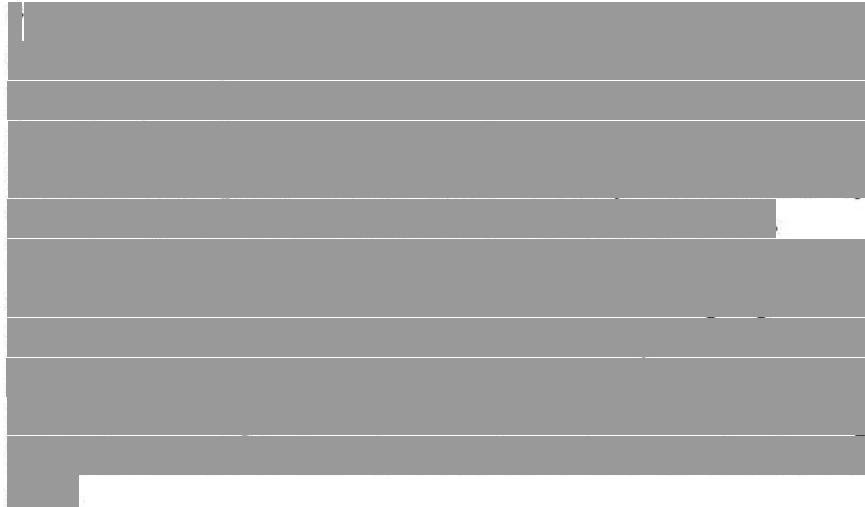
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the start of treatment. Tyvaso Label § 2.1 (“The maximum recommended dosage is 9 breaths per treatment session, 4 times daily”). Patients who tolerate the maximum allowable dose are unable to increase their dose over time as their clinical needs change and an increase in dose is required. Patients who are unable to tolerate the maximum allowable dose due to issues related to the inhaled dosage form are also unable to increase their dose over time due to the tolerability issues that limited their maintenance dose in the first place.

Unlike Tyvaso, the maximum dose of oral treprostinil “is determined by tolerability.” Orentiram Label § 2.1 (Recommended Dosing). Thus, over time, Tyvaso’s efficacy will predictably diminish as patients reach the maximum allowable dose and Orenitram’s efficacy will be maintained as higher doses are permitted. The dosing flexibility of oral treprostinil versus the dosing inflexibility of Tyvaso forms a clear basis for a plausible hypothesis that oral treprostinil may be clinically superior to Tyvaso due to greater efficacy.

As to whether prior FDA actions bear on this, the June 7, 2010 memo of Drs. Startzman and Coté granting designation to Tyvaso exclusively references safety as the basis for this designation and is wholly silent on comparative efficacy of Tyvaso and Remodulin.



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[REDACTED]

Attached are both the June 7, 2010 and May 25, 2010 memos.

B. Oral Treprostinil will have Greater Safety in the Target Population

Because of the dosing flexibility beyond the Tyvaso limits, discussed above, such flexibility presents a plausible basis to conclude that oral treprostinil may provide greater long-term safety to patients with PAH. The limiting maximal allowable dose for Tyvaso [REDACTED]

[REDACTED] Choosing off-label use of Tyvaso presents inferior safety to the on-label use of oral treprostinil because the safety issues associated with such off-label use of Tyvaso are unknown. Clinical studies of Tyvaso included patients up to 12 breaths per dose four times per day, and the approved dosing is up to 9 breaths per dose. It is unknown what the clinical safety issues are once a patient exceeds 12 breaths per dose.

In addition, because oral treprostinil does not expose the patient to safety concerns that are specific to the inhalation dosage form (e.g., cough, throat irritation, and pharyngolaryngeal pain), the oral dosage form avoids the specific adverse reactions that are particularly difficult for patients whose pulmonary system is already substantially compromised.

Therefore, once a patient has reached the maximum allowable on-label Tyvaso dose, the only available options for continued use of treprostinil [REDACTED]

[REDACTED]¹

¹ Furthermore, to my knowledge, FDA's decisions to grant designation based on a "plausible hypothesis of clinical superiority" grounded on a safety advantage has not previously required that there be a simultaneous showing of equal efficacy. While such may be a reasonable additional consideration or showing for OOPD to require in the future, going forward, it would seem to require advance notice of this type of change before being implemented. For instance, I was involved in one of the first (and maybe the first) "breaking" of exclusivity based on improved safety when OOPD recognized Avonex as safer than Betaseron (whose sponsor I represented) on grounds of injection site reactions. On behalf of Betaseron's sponsor, I urged FDA to evaluate all aspects of safety (for there was evidence of more infections with Avonex than Betaseron) as well as urged FDA to consider requiring a showing of similar or equivalent efficacy. In the case of Avonex, OOPD did not conduct an analysis of overall safety or reach a finding of equivalent efficacy.

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C. Oral Treprostinil Presents a MCTPC

In addition to the greater efficacy and greater target population safety of oral treprostinil versus Tyvaso, there are also a number of other independent bases for finding that oral treprostinil presents a MCTPC versus Tyvaso. Although we will not elaborate on these other items in detail, because, as discussed above, we believe that the dose flexibility afforded by oral treprostinil is sufficient to meet the relatively low bar when “liberally granting designation based on a plausible hypothesis of clinical superiority,” we nonetheless list, in no particular order, these other bases here for completeness.

1. [REDACTED]

[REDACTED]² Because oral treprostinil presents substantially less inconvenience, a patient has a greater ability to maintain a more normal lifestyle.

In addition to greater evidence of the beneficial impact to patients in their activities of daily living provided in this letter and based on what was presented previously by the sponsor, we note that, although your March 2012 letter disagreed with our assertion that dosing convenience presented a MCTPC, this “dosing convenience” theory alone has previously formed the basis for orphan designation. In the case of Procysbi (cysteamine bitartrate) Delayed-release Capsules, OOPD designated this drug as an orphan drug on a MCTPC theory that an extended-release tablet provided greater convenience to patients who otherwise were taking an immediate-release form of cysteamine bitartrate. There, FDA granted designation because the 6-hour IR dosing required patients to alter their sleep patterns to permit them to wake and take their required doses at the specified intervals. Here, patients who take Tyvaso similarly must carefully schedule their daily activities to time those activities to when peak benefit from inhalation occurs. This may not always be possible given that patients must schedule these inhalations at sufficiently time-separate parts of each day (that is, patients must administer the drug at the specified time, which is four times daily or

² See, e.g., The Voice of the Patient, *A series of reports from the U.S. Food and Drug Administration's (FDA's) Patient-Focused Drug Development Initiative*, at pp. 13-14 (Meeting, May 13, 2014, Report dated December 2014) (“Several participants mentioned that an ideal treatment would bypass the need for IV administration and the use of other cumbersome apparatus. . . . One web participant shared that an ideal treatment would not ‘interfere with daily life activities . . . such as not having to mix medications, stress during simple showers and sleep, change sites, or [stopping] everything to do a breathing treatment.’”), available at <http://www.fda.gov/downloads/ForIndustry/UserFeesPrescriptionDrugUserFee/UCM429382.pdf>.

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approximately every four hours during the waking hours). The burden on patients is not different from those required to wake themselves during the night to take a tablet. The twice-daily oral dosing of oral treprostinil frees patients from the need to schedule around their prescriptions and administration of an oral tablet takes mere seconds when taken with food and a glass of water – actions that can be performed virtually any time at any location without disruption of activities.

2. [REDACTED] This can substantially affect the quality of life for patients trying to maintain normalcy. (The survey data is available from the sponsor should FDA need or request the data.) The time required to administer oral treprostinil is less than one minute per day.
3. In 2013 and 2014, [REDACTED]; [REDACTED]. These complaints would be absent with oral treprostinil due to the lack of a need for a special device to administer the drug.
4. [REDACTED]
[REDACTED] No such risk exists with oral treprostinil.
5. [REDACTED]
[REDACTED] Oral treprostinil may be taken with any liquid available to the patient.⁴
6. [REDACTED]
[REDACTED] 4

³ See, e.g., The Voice of the Patient, *A series of reports from the U.S. Food and Drug Administration's (FDA's) Patient-Focused Drug Development Initiative*, at p. 8 (Meeting, May 13, 2014, Report dated December 2014) ("Participants described the significant impact of PAH symptoms on the ability to perform routine household activities. As one participant explained, 'daily activities such as cooking, washing dishes, family errands are often exhausting.'"), available at <http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM429382.pdf>.

⁴ A Tyvaso Patient Starter Kit is included with this submission. [REDACTED]
[REDACTED]

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7.

[REDACTED]
[REDACTED] No such contingencies are required for oral treprostinil.⁴

8. After administering Tyvaso, patients must dispose of the excess drug and must daily clean the various parts associated with the delivery device, such as the mouthpiece, filter, and filter shells. Oral treprostinil produces substantially less waste because the only discarded material is the drug packaging, and then it is only discarded after it is no longer needed, and no cleaning is required.⁴

9.

[REDACTED]
[REDACTED] Because oral treprostinil is simpler to administer, these patient populations are more able to take their required medication.

10.

[REDACTED]
[REDACTED] Oral treprostinil does not present such difficulties, nor does it require a patient to choose between their faith or their medications.

11. We also note that in January 2015, FDA granted a period of orphan drug exclusivity based on the approval of an NDA for Ryanodex (dantrolene sodium) Injectable Suspension (“Ryanodex”) for the treatment of malignant hyperthermia after having designated the drug based on a plausible hypothesis that Ryanodex was superior to the previously approved dantrolene sodium formulations. In that decision, OOPD accepted the plausible hypothesis that a one-minute administration rather than a one-hour administration, both by an anesthesiologist, afforded the anesthesiologist more time to concentrate on continued supportive care and treatment of the patient and that this, in turn, would have a contribution to patient care. In the instant case, the dosing flexibility (not to mention the other considerations listed above) of oral treprostinil exceeds the Ryanodex standard for MCTPC. With Ryanodex, the hypothesized contribution to patient care was attenuated and based on no data other than the reasoning that the time benefit to the anesthesiologist would be expected to translate to increased patient care by the anesthesiologist. Here, we know that PAH patients will require ever-higher doses of treprostinil and we know that patients dose out of the ability to use Tyvaso and must resort to IV/SC treprostinil. We also know that oral treprostinil affords patients the ability to escalate dosing as needed to treat symptoms without the need to change dosage forms. Here, we know that all the MCTPC benefits in saving time and not needing to coordinate dosing with periods of expected activity are all benefits that accrue directly to the patient themselves, and not indirectly as

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hypthesized benefits from a healthcare provider having the mere “potential” to confer more attention to the patient. Thus, the plausible contribution to patient care here is much more than the hypothetical indirect basis that allowed for Ryanodex designation (and exclusivity).

[REDACTED]

[REDACTED]

[REDACTED]

III. Orphan Drug Exclusivity for Oral Treprostinil

UTC understands that OOPD has created a regulatory scheme that is intended to encourage innovation in the treatment of orphan disease while also protecting the incentives already granted to earlier innovators.

Accordingly, FDA has historically required that a subsequent applicant for orphan designation and exclusivity demonstrate clinical superiority based on improved efficacy via head-to-head studies that meet FDA’s requirements for product superiority labeling. This policy, however, must account for instances where greater efficacy is essentially self-evident. Here, the fact that PAH patients hit a ceiling on prostacyclin dose using Tyvaso when PAH patients will require increasing doses of prostacyclin plus the fact that oral treprostinil has no such ceiling for dosing means that oral treprostinil is *de facto* clinically superior by permitting PAH patient to access the increasing doses they require.

[REDACTED]

We further acknowledge that, orphan product designations and exclusivities granted under 21 C.F.R. § 316.20(b)(5) can present “takings issues” under Constitutional law which can prove to be problematic for FDA. Specifically, if exclusivity is granted to one company for a drug to treat a specific disease, granting another company exclusivity for the same drug treating the same disease could be viewed as taking of a property right (the right to exclusively market the drug for the disease) from one company to the benefit of another without compensating the first company for the taking. In the event that subsequent designations for the same drug with the same indication are sought by the same sponsor (as is the case here) there are no Constitutional “takings” concerns, as the government is not depriving any individual or entity the exclusivity granted to the earlier product. Stated another way, when FDA created the rules on granting designation to a second version of the same drug for the same rare use, FDA only wanted to do so in the case in which the patient community would clearly be accessing a superior therapy because otherwise FDA designation of the second product may have been challenged by the first product’s sponsor as a violation of the first sponsor’s property right. However,

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what FDA's rules did not account for is the exceptional case in which the second product is developed by the same sponsor and, therefore, there is no risk of a "takings" scenario or concern. In fact, the first sponsor is the one who knows the molecule the best as well as knows the needs of this patient community and is in the best position to create a superior product to benefit those patients. So, incentivizing such sponsors would further the interests of the patient community without risk of Constitutional or other exclusivity challenges. Furthermore, there is no "evergreening" issue here either because, as this case illustrates, once Tyvaso's orphan drug exclusivity expires, generics of Tyvaso would not be barred by any orphan drug exclusivity for oral treprostinil.

Stating this as a corollary policy matter, FDA **should** incentivize companies to identify product improvements that advance orphan patient care. When there is no competitor exclusivity involved, there are no overriding policy considerations of fairness to the earlier-designated product that would heighten the burden of proof for the subsequent designation. FDA could consider articulating this in a formal policy statement.

Finally, there is no potential for "evergreening" presented here. First, even if OOPD grants Orenitram designation, such would have no impact on availability of generic versions of Remodulin and Tyvaso. As for such designation leading to exclusivity for Orenitram, again there is no public health issue because if Orenitram is superior to Tyvaso (and Remodulin), then the incentive and exclusivity are exactly those for which this system was created by OOPD (and alternatively, even if there are some who may regard such designation as an error because Orenitram is not superior to Tyvaso, then generic versions of Tyvaso would meet the needs of PAH patients if indeed Orenitram is not truly superior).

Thus, the data and information presented above are sufficient for FDA to designate oral treprostinil as an orphan drug. As for "breaking" the Tyvaso exclusivity, that is not a consideration here as the sponsor is the same and would constructively "waive" Tyvaso's exclusivity with respect to the same sponsor's oral product. Stated another way, in this case, FDA need not establish precedent regarding the breaking of a prior exclusivity because UTC, under Section 527(b)(2) of the Act, would constructively (or formally, if necessary) waive the Tyvaso exclusivity with respect to granting exclusivity for the oral treprostinil dosage form. As such, there is neither a policy nor legal barrier with respect to subsequent exclusivity for the oral therapy that should result in OOPD applying a greater level of scrutiny to the pending designation request.

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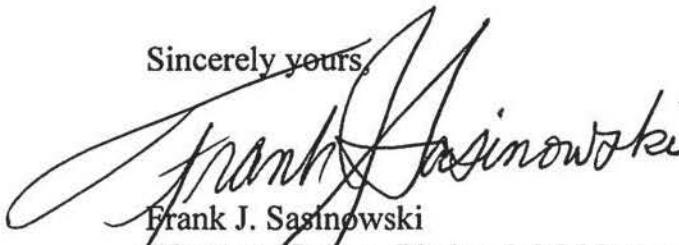
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The scientific evidence (see, e.g., Appendix 1), patient considerations, and information presented here demonstrate both that the prevalence of PAH meets the requirements for orphan drug designation, and that there is a plausible hypothesis that Orenitram may be clinically superior to Tyvaso. Should OOPD designate Orenitram an orphan drug, UTC will waive Tyvaso exclusivity with respect to Orenitram. Therefore, if OOPD did “liberally grant[] designation [of Orenitram] based on a plausible hypothesis of clinical superiority,” then OOPD would not need to struggle with how to determine whether that “plausible hypothesis” had been established sufficiently to “break” Tyvaso’s exclusivity because Tyvaso’s exclusivity would be waived with respect to Orenitram.

Please do not hesitate to contact me if you have any questions or if you would like to discuss this matter further. We look forward to your consideration of our renewed and augmented request.

Sincerely yours,



Frank J. Sasnowski
Director, Hyman, Phelps & McNamara, P.C.
Counsel for United Therapeutics Corporation

Enclosures

FJS/KRK/JWC/

cc: Dean Bunce
 Paul Mahon
 United Therapeutics Corporation

EXHIBIT 4



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
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M E M O R A N D U M

From: Donna Snyder, MD, Medical Officer
Pediatric and Maternal Health Staff (PMHS)

Through: Hari Cheryl Sachs, MD, Team Leader
Lynne Yao, MD, OND Associate Director,
Pediatric and Maternal Health Staff (PMHS)

To: Division of Neurology Products (DNP)

NDA: 20622

Drug: Glatiramer acetate injection (Copaxone®)
Sponsor: Lundbeck, Inc.

Approved indications: Reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis (RRMS), including patients who have experienced a first clinical episode and have MRI features consistent with MS.

Consult Question: PMHS was asked to attend team meetings for this efficacy supplement to the NDA and assist with preparation of the Pediatric Review Committee (PeRC) paperwork.

Materials Reviewed

- PMHS consult request dated March 29, 2013, (DARRTS Reference ID: 3285153)
- Pediatric waiver request submitted by the sponsor on March 29, 2013

- Copaxone® (glatiramer acetate injection) labeling from Drugs@ FDA
- Cross-Discipline Team Leader Review and Medical Review dated February 26, 2006 to expand indication to include patients who have had a first clinical episode of MS and have MRI features consistent with MS
- Approval letters from Drugs@FDA for Aubagio (teriflunomide, NDA 202992), Gilenya® (fingolimod, NDA 22527) and Tecfidera (dimethyl fumarate, NDA 204063)
- PMHS consult review by B. Durmowicz, dated March 28, 2012, (DARRTS Reference ID: 3113986)

Background and Regulatory History: originally approved on December 20, 1996.

Glatiramer acetate injection (Copaxone®) is indicated for the reduction of frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis (RRMS), including patients who have had a first clinical episode and have MRI features consistent with MS. Glatiramer acetate consists of the acetate salts of synthetic polypeptides containing the amino acids L-glutamic acid, L-alanine, L-tyrosine, and L-lysine. The drug is thought to act by modifying the immune processes that are responsible for Multiple Sclerosis (MS), however the exact mechanism of action is not known.

Glatiramer acetate injection (Copaxone®) was approved on December 20, 1996, for the treatment of RRMS. Glatiramer acetate was originally granted orphan status; however this orphan designation expired on December 20, 2003. The original approval predates the Pediatric Research and Equity Act (PREA). On February 27, 2009, the indication was expanded to allow treatment of patients with RRMS who have experienced a first clinical episode and have MRI features consistent with MS. DNP determined that PREA did not apply since this was an expansion of the current indication and not a new indication.

On March 29, 2013, the sponsor submitted a supplemental application to the NDA containing study data to support modifying the dosing regimen. Currently, glatiramer acetate is dosed subcutaneously at 20 mg once a day (QD) using a 20 mg/ml formulation. This supplement includes data to support dosing at 40 mg subcutaneously three times a week (TIW) with a more concentrated 40 mg/ml dosage form. According to PREA, section 505B(a) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 355a], any application which includes a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration is required to submit a pediatric assessment or a request for a waiver of pediatric studies. This supplemental application triggers PREA as a new dosing regimen. (b)(4)

The applicant has not conducted any studies in the pediatric population to date.

Of note, a pediatric Written Request (WR) was issued on January 3, 2000, but was declined by the sponsor. In December 2011, the sponsor submitted a (b)(4) (b)(4) (b)(4)

(b) (4)

(b) (4)

Discussion:

The criteria for a full or partial waiver under the Pediatric Research and Equity Act (PREA) are the following:

1. Necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed).
2. The product would be ineffective or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information must be included in labeling.
3. The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

In addition, a partial waiver can be granted if the applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed. If ultimately, the sponsor cannot produce an appropriate pediatric formulation, the partial waiver will only include those age ranges that would require a different formulation. The information on the sponsor's attempts to produce an appropriate pediatric formulation will be posted publically on the FDA website.

The sponsor's rationale for the (b) (4) is that studies are impossible or highly impracticable because of the low prevalence of the disease in the pediatric population and supplied epidemiologic data on prevalence to support the assertion.

(b) (4) a partial waiver would be appropriate for pediatric patients from birth to 9 years of age because necessary studies are impossible or highly impracticable. This is because the number of pediatric patients less than 10 years of age with multiple sclerosis is too small. However, based on discussions with academia, DNP has determined that studies in MS in pediatric patients ages 10 to 17 years of age are possible and that studies will provide a public health benefit, especially since there are no approved therapies for pediatric patients with MS.¹ This requirement for studies is evidenced by the current PREA postmarketing requirements (PMRs) for Aubagio® (teriflunomide, NDA 202992), Gilenya® (fingolimod, NDA 022527) and Tecfidera® (dimethyl fumarate, NDA 204063).

Additionally, in the case of glatiramer acetate, there are no specific safety concerns that preclude a study in the pediatric population. Glatiramer acetate is currently used off-label

¹ Chitnis T et al. International Pediatric MS Study Group Clinical Trials Summit: meeting report. Neurology: 2013. Mar 19;80(12):1161-8.

in pediatric patients with MS as first-line therapy and is relatively well tolerated.² Studies for glatiramer acetate are needed in the pediatric population to confirm that dosing is appropriate and that glatiramer acetate is efficacious in the pediatric population. DNP will require a study in for pediatric patients with MS 10 to 17 years of age and will request that the sponsor submit a plan and timelines for the study. PMHS concurs that none of the criteria for a partial waiver apply for pediatric patients between 10 and 16 years of age and agrees that a study should be performed under PREA.

Conclusion:

PMHS participated in the filing, mid-cycle and wrap-up meetings and assisted DNP with the review of the paperwork needed for the Pediatric Review Committee (PeRC) Meeting. DNP met with the PeRC on December 4, 2013. PeRC agreed to the pediatric plan for a partial waiver for pediatric patients ages 0 to 10 years of age and to a deferral of pediatric studies for ages 10 to 17 years of age because the product is ready for approval in adults before pediatric studies have been completed. PeRC recommended that DNP determine whether a juvenile toxicology study is needed for the product and if a study is not needed, that the proposed timelines be moved up. PeRC also recommended that the division consider issuing a Written Request to the sponsor to encourage completion of studies under PREA. However, this reviewer notes that the sponsor's patents will expire in May 2014, so completion of studies in order to be eligible for any additional exclusivity will not likely be feasible.

² Yeh, A. Management of Children with Multiple Sclerosis. *Pediatric Drugs* 2102; 14 (3): 165-177.

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/s/

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12/19/2013

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12/22/2013