DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
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MAR 10 2014

Dean Bunce
Executive Vice President
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United Therapeutics Corp.
P.O. Box 14186
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Re: Docket No. FDA-2013-P-1293

Dear Mr. Bunce:

This letter responds to the citizen petition submitted to the Food and Drug Administration (FDA or the Agency) by United Therapeutics Corp. (UT), dated October 15, 2013 (Petition). In the petition, you request that FDA refrain from approving any abbreviated new drug application (ANDA) for a generic version of Remodulin (treprostinil) Injection if the ANDA includes proposed labeling that omits or carves out the information in Remodulin's approved labeling about the administration of intravenous (IV) treprostinil with a high pH glycine diluent. The petition maintains that a generic treprostinil injection product that omits this information from its labeling would be less safe than Remodulin for the treatment of pulmonary arterial hypertension (PAH).[1]

The Agency has carefully reviewed the information in your petition and the comment submitted to the public docket by Olsson Frank Weeda Terman Matz PC on behalf of Sandoz, Inc. For the reasons set forth below, your petition is denied.

I. BACKGROUND

A. Remodulin

UT is the sponsor of the new drug application (NDA) for Remodulin (treprostinil) Injection (NDA 021272), a prescription drug product indicated for the treatment of PAH to diminish the symptoms associated with exercise. The active ingredient in Remodulin is treprostinil, a synthetic prostacyclin analog with vasodilatory effects. FDA approved UT's NDA for Remodulin Injection on May 21, 2002.[2]

[1] PAH is a rare disorder characterized by abnormally high blood pressure in the pulmonary arteries. If it is not treated, the right side of the heart will become overworked and eventually fail.

[2] Information pertaining to the approval of Remodulin (treprostinil) Injection is available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-272_Remodulin.cfm (last accessed Feb. 27, 2014).

Remodulin can be administered as a continuous subcutaneous infusion or a continuous IV infusion via an indwelling central venous catheter. FDA approved the latter route of administration in 2004 as an alternative for patients who are unable to tolerate a subcutaneous infusion.[3] At that time, the labeling stated that intravenously administered Remodulin must be diluted with either Sterile Water for Injection or 0.9% Sodium Chloride Injection, both of which have a neutral pH.[4] FDA has since approved Sterile Diluent for Flolan and Sterile Diluent for Epoprostenol Sodium as acceptable diluents for use in the administration of IV Remodulin.[5] Both of these diluents have a high pH.

UT has listed four patents for Remodulin in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book). Only one of the four patents, U.S. Patent No. 7,999,007 (the '007 patent), is relevant to the issues raised in the petition. The '007 patent was issued on August 16, 2011, and expires on March 29, 2029. It is listed in the Orange Book with use code U-1437, which describes the following method of use: "Administration of Remodulin diluted for intravenous infusion with Sterile Diluent for Flolan or Sterile Diluent for Epoprostenol Sodium prior to administration."

B. Labeling Changes Related to the Administration of IV Treprostinil

In 2007, FDA received a report from the Centers for Disease Control and Prevention (CDC) that suggested there was an increased potential for bloodstream infections (BSIs) associated with the administration of IV treprostinil. The report contained the CDC's findings from a retrospective investigation of seven PAH treatment centers that had been conducted to determine the relative rates of BSIs in patients who had been treated with IV treprostinil or IV epoprostenol between 2003 and 2006. Among other things, the CDC found that the treatment centers' pooled mean rates of BSIs during the period of investigation were significantly higher for IV treprostinil patients than they were for IV epoprostenol patients.[6]

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[3] Information pertaining to FDA's approval of the IV route of administration for Remodulin is available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/021272Orig1s002.pdf (last accessed Feb. 27, 2014).

[4] Approved Labeling for Remodulin Injection at 9-10 (Nov. 24, 2004), available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/021272Orig1s002.pdf (last accessed Feb. 27, 2014).

[5] FDA approved the addition of Sterile Diluent for Flolan to Remodulin's labeling in September 2008. See Letter to Kerry McKenzie, United Therapeutics Corp., from Norman Stockbridge, M.D., Ph.D., Director, Division of Cardiovascular and Renal Products, Office of Drug Evaluation I, Center for Drug Evaluation and Research (Sept. 12, 2008), available at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2008/021272s008ltr.pdf (last accessed Feb. 27, 2014). The addition of Sterile Diluent for Epoprostenol Sodium to the labeling was approved in September 2013. See Letter to Rex Mauthe, United Therapeutics Corp., from Mary Ross Southworth, PharmD., Deputy Director for Safety, Division of Cardiovascular and Renal Products, Office of Drug Evaluation I, Center for Drug Evaluation and Research (Sept. 26, 2013), available at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2013/021272Orig1s020ltredt.pdf (last accessed Feb. 27, 2014).

[6] Department of Health and Human Services, CDC, Bloodstream Infections Among Patients Treated with Intravenous Epoprostenol or Intravenous Treprostinil for Pulmonary Arterial Hypertension — Seven Sites, United States, 2003-2006, 56:8 MMWR 170, 170-72 (Mar. 2, 2007).

In light of the CDC's finding, the labeling for Remodulin was revised in February 2008 to discourage the use of the IV route of administration. The updated labeling advised healthcare providers that they should administer treprostinil injection as a subcutaneous infusion when tolerated by patients because it has fewer risks than an IV infusion.[7] In 2010, the labeling was revised again, in part, to further emphasize that subcutaneous infusion is the preferred route of administration.[8]

Most recently, the labeling for Remodulin was revised in September 2013 to add information related to the use of high pH diluents in IV infusions of treprostinil. Specifically, the following statement was added to the end of Section 5.1 of the labeling: "Administration of IV Remodulin with a high pH glycine diluent such as Sterile Diluent for Flolan or Sterile Diluent for Epoprostenol Sodium has been associated with a lower incidence of BSIs when compared to neutral diluents (sterile water, 0.9% sodium chloride) when used along with catheter care guidelines."[9] Sterile Diluent for Epoprostenol Sodium was also added to the labeling as an acceptable diluent for use in IV infusions. The current list of acceptable diluents comprises Sterile Water for Injection, 0.9% Sodium Chloride Injection, Sterile Diluent for Flolan, and Sterile Diluent for Epoprostenol Sodium.[10]

C. Abbreviated Approval Pathway for Generic Drugs (ANDAs)

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) created section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)). The Hatch-Waxman Amendments reflect Congress's efforts to balance the need to "make available more low cost generic drugs by establishing a generic drug approval procedure for pioneer drugs first approved after 1962" with new incentives for drug development in the form of marketing exclusivity and patent term extensions.[11] Section 505(j) of the FD&C Act established an abbreviated approval pathway for a drug product that is the same as a previously approved drug (the reference listed drug or RLD) with respect to active ingredient, dosage form, route of administration, strength, and, with certain exceptions, labeling and conditions of use, among other characteristics. An ANDA applicant also must demonstrate that its proposed product is bioequivalent to the RLD. An applicant that

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[7] Approved Labeling for Remodulin Injection at 4 (Feb. 4, 2008), available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021272s009lbl.pdf (last accessed Feb. 27, 2014).

[8] See Letter to Kerry McKenzie, United Therapeutics Corp., from Norman Stockbridge, M.D., Ph.D., Director, Division of Cardiovascular and Renal Products, Office of Drug Evaluation I, Center for Drug Evaluation and Research (Jan. 8, 2010) (describing labeling changes), available at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/021272s011ltr.pdf (last accessed Feb. 27, 2014).

[9] Approved Labeling for Remodulin Injection at 7 (Sept. 26, 2013), available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021272s020lbledt.pdf (last accessed Feb. 27, 2014).

[10] Id. at 4.

[11] See House Report No. 98-857, part 1, at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647 at 2647-2648.

meets the requirements under section 505(j) for approval may reference the Agency's finding of safety and effectiveness for the RLD and need not repeat the extensive nonclinical and clinical investigations required for approval of a stand-alone NDA submitted under section 505(b)(1) of the FD&C Act.

An ANDA applicant is subject to applicable periods of marketing exclusivity granted to the RLD and is required to submit an appropriate patent certification or statement for each patent that claims the RLD or a method of using the RLD for which the applicant is seeking approval and for which information is required to be filed under section 505(b)(1) or 505(c)(2) of the FD&C Act (see section 505(j)(2)(A)(vii)-(viii) of the FD&C Act).[12]

D. Legal Authority for Labeling Differences Between ANDAs and NDAs Based on Patent Claims

1. Patent Listing and Certification Requirements

Section 505(b)(1) of the FD&C Act requires NDA applicants to file as part of the NDA "the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or *which claims a method of using such drug* and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug" (emphasis added).[13] FDA is required to publish the patent information provided by the NDA holder for drugs approved under 505(c) and does so in the Orange Book (section 505(b)(1), (c)(2), and (j)(7) of the FD&C Act, and 21 CFR 314.53(e)).

For each unexpired patent listed in the Orange Book, the ANDA applicant must submit either a paragraph III certification (delaying approval until the date on which such patent will expire), a paragraph IV certification (certifying that such patent is invalid or will not be infringed by the manufacture, use, or sale of the drug product for which the ANDA is submitted), or, with respect to a method of use patent, a statement that the patent does not claim a use for which the ANDA applicant is seeking approval (section 505(j)(2)(A)(vii)-(viii) of the FD&C Act).

An ANDA applicant seeking to omit an approved method of use covered by a listed patent need not file a paragraph III or IV certification for that patent. Instead, the applicant may submit a "section viii statement" acknowledging that a given method of use patent has been listed, but stating that the patent at issue does not claim a use for which the applicant seeks approval (see section 505(j)(2)(A)(viii) of the FD&C Act). Such a statement requires the ANDA applicant to omit or "carve out" from its labeling

[12] Marketing exclusivity is not at issue here, so this response does not address the effect of exclusivity on ANDA approval but focuses, instead, on relevant patent protection.

[13] Section 505(c)(2) of the FD&C Act imposes an additional patent submission requirement on holders of approved NDAs when those NDA holders subsequently obtain new patent information that could not have been submitted with the NDA.

information pertaining to the protected use (21 CFR 314.92(a)(1) and 314.94(a)(12)(iii)(A)). Section 314.94(a)(12)(iii)(A) states that:

> If patent information is submitted under section 505(b) or (c) of the [A]ct and § 314.53 for a patent claiming a method of using the listed drug, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent, [the ANDA applicant must submit] a statement explaining that the method of use patent does not claim any of the proposed indications.[14]

If an ANDA applicant files a section viii statement, the patent claiming the protected method of use will not serve as a barrier to ANDA approval.[15] This right to file a section viii statement and carve out from labeling method-of-use information protected by a patent has been upheld by the courts.[16]

2. Labeling Requirements for Products Approved as ANDAs

Section 505(j)(2)(A)(i) of the FD&C Act requires that an ANDA contain "information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a [listed drug]." This language reflects Congress's intent that a generic drug be safe and effective for each "condition of use" prescribed, recommended, or suggested in the generic drug labeling. However, it does not require that an ANDA be approved for each condition of use for

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[14] Although FDA regulations use the term "indications" to refer to information an ANDA applicant omits from its labeling in the context of submitting a statement that a protected use of a drug is not claimed in a listed patent (§ 314.94(a)(12)(iii)), the preambles for the proposed rule and final rule on patent and exclusivity provisions related to ANDA approval express no intent to distinguish between method of use and indication (see, e.g., 59 FR 50338 at 50347 (October 3, 1994) (using "indications" and "method of use" interchangeably)). The preamble to the final rule emphasizes that an ANDA applicant does not have the option of choosing between a paragraph IV certification and a section viii statement; where the labeling does not include the indication, only the section viii statement is appropriate (id.). In addition, the preamble to the proposed rule states that if "the labeling for the applicant's proposed drug product does not include any indications that are covered by the use patent," then the ANDA applicant would submit a section viii statement rather than a paragraph IV certification (54 FR 28872 at 28886 (July 10, 1989)).

[15] The Agency's interpretation of the plain language of the FD&C Act is further supported by Congressional intent, as evidenced by the passage below:

> . . .The [ANDA] applicant need not seek approval for all of the indications for which the listed drug has been approved. For example, if the listed drug has been approved for hypertension and angina pectoris, and if the indication for hypertension is protected by patent, then the applicant could seek approval for only the angina pectoris indication.

H.R. Rep. No. 857 (Part I), 98th Cong., 2d sess. 21.

[16] See *Purepac Pharmaceutical Company v. Thompson*, 354 F.3d 877, 880 (D.C. Cir. 2004) (stating that a "section viii statement indicates that a patent poses no bar to approval of an ANDA because the applicant seeks to market the drug for a use other than the one encompassed by the patent"); *Torpharm, Inc. v. Thompson*, 260 F. Supp. 2d 69, 73 (D.D.C. 2003) (stating that a section viii statement "avers that the patent in question has been listed, but does not claim a use for which the applicant seeks FDA approval").

which the RLD is approved. In § 314.92(a)(1), FDA explicitly states that a proposed generic drug product must have the same conditions of use as the listed drug, except that "conditions of use for which approval cannot be granted because of exclusivity or an existing patent may be omitted."

The FD&C Act also requires that an ANDA contain "information to show that the labeling proposed for the new [generic] drug is the same as the labeling approved for the listed drug . . . except for changes required because of differences approved under a petition filed under [section 505(j)(2)(C)] or because the new drug and the listed drug are produced or distributed by different manufacturers" (section 505(j)(2)(A)(v) of the FD&C Act; see also 21 CFR 314.94(a)(8)(iv)). A parallel provision appears in section 505(j)(4)(G) of the FD&C Act.[17] Section 314.94(a)(8)(iv) sets forth examples of permissible differences in labeling that may result because the generic drug product and RLD are produced or distributed by different manufacturers. These differences include the following:

> . . . differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or *omission of an indication or other aspect of labeling protected by patent* [emphasis added] or accorded exclusivity under section 505(j)(5)(F) of the [FD&C A]ct.

Our regulations further provide that to approve an ANDA containing proposed labeling that omits "aspects of the listed drug's labeling [that] are *protected by patent* [emphasis added]," we must find that the "differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, nonprotected conditions of use" (21 CFR 314.127(a)(7)). FDA has affirmed its authority to approve generic drug products with labeling that omits protected information on many occasions.[18]

Relevant case law affirms an ANDA applicant's ability to carve out protected labeling without violating the "same labeling" requirement. For example, in *Bristol Myers Squibb v. Shalala*, F.3d 1493, 1500 (D.C. Cir. 1996), the D.C. Circuit ruled that "the statute expresses the legislature's concern that the new generic be safe and effective for each indication that will appear on its label; whether the label for the new generic lists every indication approved for the use of the pioneer is a matter of indifference." Similarly, in *Sigma-Tau Pharmaceutical, Inc. v. Schwetz*, 288 F.3d 141, 148, fn. 3 (4th Cir. 2002), the Fourth Circuit upheld the right of an ANDA applicant to carve out an indication protected by orphan drug exclusivity as a permissible difference because of a difference in manufacturer.

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[17] Section 505(j)(4)(G) of the FD&C Act provides that FDA must approve an ANDA unless, among other things, "the information submitted in the application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for [the RLD] except for changes required because of differences approved under [an ANDA suitability petition] or because the drug and the listed drug are produced or distributed by different manufacturers."

[18] See, e.g., Letter to Stephen Auten, Vice President, Sandoz, Inc., from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research (July 30, 2010), Docket No. FDA-2010-P-0087.

Thus, under the FD&C Act, FDA regulations, and applicable case law, an ANDA applicant can omit an indication or other aspect of the RLD's labeling that is protected by a listed patent if the omission does not render the proposed generic drug product less safe or effective than the RLD for the conditions of use that remain in the labeling.

II. DISCUSSION

Your petition requests that FDA refrain from approving any ANDA for a generic version of Remodulin Injection if the ANDA includes proposed labeling that omits information about how the administration of IV treprostinil with a high pH glycine diluent has been associated with a lower incidence of BSIs compared to neutral diluents when used along with catheter care guidelines (Petition at 2). You state that at least one ANDA applicant, Sandoz, Inc., has publicly indicated that it will seek such a carve-out from the labeling for its proposed generic treprostinil injection product (Petition at 2, 6). We address below your assertions in support of the requested action.

A. Omission of Information About the Administration of IV Treprostinil With a High pH Glycine Diluent Would Not Render a Generic Treprostinil Injection Product Less Safe Than Remodulin

You contend that FDA cannot lawfully approve an ANDA that proposes to carve out the statement in Remodulin's labeling about how the administration of IV treprostinil with a high pH glycine diluent has been associated with a lower incidence of BSIs (i.e., the last sentence of Section 5.1 of Remodulin's labeling) because such a carve-out would render the proposed generic product less safe than Remodulin (Petition at 1-2, 7-8).[19] You maintain that the approval of a generic treprostinil injection product with labeling that omits this statement, which you claim is protected by the '007 patent, would "expose patients to an unreasonably increased risk of potentially fatal BSIs" (Petition at 2). You also claim that many healthcare providers will be unaware that they can reduce the risk of BSIs through the choice of diluent if FDA approves a treprostinil injection ANDA with labeling that omits information about the administration of IV treprostinil with a high pH glycine diluent (Petition at 8). For the reasons set forth below, we disagree.

As a preliminary matter, there is always a risk of BSIs whenever treprostinil is administered by IV infusion, regardless of the diluent used, because it involves the use of an indwelling central venous catheter. Indeed, the risk of BSIs is the main reason why the labeling for Remodulin was revised in 2008 to discourage healthcare providers from administering treprostinil as an IV infusion.[20] The first paragraph of Section 5.1 of the current labeling explains that "continuous subcutaneous infusion (undiluted) is the preferred mode of administration" because "[the IV] route is associated with the risk of blood stream infections (BSIs) and sepsis, which may be fatal." Similarly, the second

[19] Aside from the removal of the last sentence of Section 5.1 of Remodulin's labeling, the petition does not claim that there are other labeling carve-outs necessitated by the '007 patent that would render a generic treprostinil injection product less safe or effective than Remodulin.

[20] See Section I.B.

paragraph of Section 1.1 of the current labeling advises healthcare providers that the IV route of administration "should be reserved for patients who are intolerant of the subcutaneous route, or in whom [the risks associated with chronic indwelling central venous catheters, including serious BSIs,] are considered warranted." We believe that these paragraphs adequately inform physicians of the risks posed by the IV administration of treprostinil, including the risk of BSIs, and that they are more important to the safe use of treprostinil injection than the protected information in Section 5.1 of Remodulin's labeling about the administration of IV treprostinil with a high pH glycine diluent.

We also note that the patent-protected labeling statement at issue does not, as you assert, advise healthcare providers on "the use of IV treprostinil with a high pH glycine diluent *to reduce the risk of BSIs*" (Petition at 7, emphasis added). Your assertion that it does so conflates the '007 patent's claims with the last sentence in Section 5.1 of the approved labeling for Remodulin. Although the '007 patent may claim that the administration of IV treprostinil with a high pH glycine diluent reduces the risk of BSIs,[21] Section 5.1 of the labeling is equivocal on this point. It does not say that a high pH glycine diluent will reduce the risk of BSIs in an IV treprostinil patient. Rather, it says only that the administration of IV treprostinil with a high pH glycine diluent has been *associated with* a lower incidence of BSIs when compared to neutral diluents when used along with catheter care guidelines.[22]

More to the point, the Agency does not agree that a generic treprostinil injection product with labeling that omits information about the administration of IV treprostinil with a high pH glycine diluent will "put patients at risk" (Petition at 1). When we approved the addition of this information to Remodulin's labeling in September 2013, we did so in the interest of providing healthcare providers with up-to-date information on the use of high pH glycine diluents and not out of concern that the administration of IV treprostinil with a neutral diluent should always be avoided because it poses a risk to patients. If the Agency had been concerned about the safety of neutral diluents, it could have revised the labeling to require the use of high pH glycine diluents only and taken steps to raise awareness about the effect that choice of diluent has on the risk of BSIs. We did not take these actions at the time, however, because we determined that the neutral diluents remained acceptable for use in the administration of IV treprostinil.

Furthermore, we find there is insufficient evidence that using a high pH glycine diluent instead of a neutral diluent reduces the risk of BSIs in patients being treated with IV treprostinil. Your support for this proposition comes from the studies by Zaccardelli et al. (2010)[23] and Rich et al. (2012)[24] (Petition at 5-8). The study by Zaccardelli et al. found that the antimicrobial effectiveness of treprostinil diluted with Sterile Diluent for

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[21] FDA takes no position on the validity of the '007 patent or any of its claims.

[22] Approved Labeling for Remodulin Injection at 7 (Sept. 26, 2013), available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021272s020lbledt.pdf (last accessed Feb. 27, 2014).

[23] Zaccardelli D., et al., Stability and Antimicrobial Effectiveness of Treprostinil Sodium in Sterile Diluent for Flolan, 64:7 *Int'l J. Clin. Pract.* 885, 885-91 (June 2010).

[24] Rich J.D., et al., The Effect of Diluent pH on Bloodstream Infection Rates in Patients Receiving IV Treprostinil for Pulmonary Arterial Hypertension, 141:1 *Chest J.* 36-42 (Jan. 2012).

Flolan was superior to that of treprostinil diluted with sterile saline. Subsequently, Rich et al. found that there were fewer incidences of gram negative BSIs in patients who had received IV treprostinil with Sterile Diluent for Epoprostenol Sodium compared to patients who had received IV treprostinil with a neutral diluent.

We agree that the Zaccardelli and Rich studies are appropriate for consideration by healthcare providers because they are suggestive that the administration of IV treprostinil with a high pH glycine diluent has been associated with a lower incidence of BSIs. Nonetheless, we find that these studies fall short of providing conclusive evidence that high pH glycine diluents are *in fact* superior to neutral diluents at preventing BSIs. Most significantly, neither study meets the Agency's standard for an adequate and well-controlled study (see 21 CFR 314.126).[25] For example, both studies' findings were based, in part, on a comparison to historical controls. FDA generally does not accept findings based on comparisons to historical controls as reliable evidence, however, except in special circumstances that do not apply here (see 21 CFR 314.126(b)(2)(v)). In addition, the finding by Zaccardelli et al. is not based on observations from a clinical trial that involved actual conditions of use, but rather on analyses of the change in microbial concentrations over time in CADD Medication Cassette Reservoirs filled with treprostinil diluted with Sterile Diluent for Flolan. We also view the findings from the Rich study with caution. Among other shortcomings, as Rich et al. admit, the findings were based on a comparison to a historical control cohort for IV treprostinil diluted with a neutral diluent that predated the newest catheter care guidelines, and the study did not account for possible differences among the patient cohorts regarding catheter care.

In short, we find that a generic treprostinil injection product, when labeled to exclude the information protected by the '007 patent, will not be less safe or effective than Remodulin for the treatment of PAH to diminish the symptoms associated with exercise (i.e., the nonprotected conditions of use) (see 21 CFR 314.127(a)(7)). The Agency is not convinced by the available evidence that the administration of IV treprostinil with a high pH glycine diluent is safer than administration with a neutral diluent. Further, we believe that Sterile Water for Injection and 0.9% Sodium Chloride Injection, both of which have been listed as acceptable diluents in Remodulin's labeling since FDA first approved the IV route of administration, remain safe for use in the administration of IV treprostinil. Accordingly, we will not refrain from approving an ANDA for treprostinil injection on the basis that its labeling does not include information about the administration of IV treprostinil with a high pH glycine diluent.

B. Agency Precedent Does Not Support Your Petition

You contend that in comparable circumstances, FDA has determined it cannot approve an ANDA with labeling that omits protected information (Petition at 9-10). In support of this contention, you cite two citizen petition responses in which the Agency granted a

[25] The Agency usually requires at least two adequate and well-controlled studies, each convincing on its own, to establish that a particular therapy is effective. See the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998), available at http://www.fda.gov/downloads/UCM072008.pdf (last accessed Feb. 27, 2014).

request to disallow a proposed labeling carve-out. We find that neither of the responses supports your petition.

The first citizen petition response you cite involved a proposed carve-out from the labeling for Colcrys (colchicine) tablets (Petition at 9).[26] The protected information at issue in the Colcrys petition related to the dosing regimen for colchicine for treatment of acute gout flares. FDA granted a 3-year period of exclusivity to Colcrys based on a new clinical investigation demonstrating that a lower dose regimen of colchicine for treatment of acute gout flares was as effective as the standard higher dose regimen, and resulted in significantly fewer adverse events. Although the 3-year exclusivity was limited to treatment of acute gout flares, FDA considered whether omission of certain labeling information regarding treatment of acute gout flares would render a proposed "duplicate" of Colcrys less safe or effective than Colcrys for prophylaxis of gout flares in the event that a healthcare provider determined that it was necessary to use colchicine for treatment of an acute gout flare in a patient receiving colchicine for prophylaxis and granted, in part, the petitioner's request.

The circumstances here are different from the circumstances in the Colcrys petition. Unlike the scenario described in the Colcrys petition, a patient being treated for PAH to diminish the symptoms associated with exercise would not need to consider the risk of cumulative toxicity with treprostinil if the labeling for generic products were to omit the information in Remodulin's labeling about the administration of IV treprostinil with a high pH glycine diluent.

The second citizen petition response you cite involved a proposed carve-out from the labeling for Rapamune (sirolimus) (Petition at 9-10).[27] Rapamune was approved as an immunosuppressive agent for the prophylaxis of organ rejection in patients receiving renal transplants, and was originally for use in a regimen including cyclosporine and corticosteroids. However, Rapamune and cyclosporine were found to be associated with increased renal function impairment. Based on the results of an adequate and well-controlled clinical trial, the labeling for Rapamune was revised to add information about cyclosporine withdrawal procedures in patients at low to moderate risk for rejection. Those changes received three years of exclusivity protection under section 505(c)(3)(D)(iv) of the FD&C Act.[28] Rapamune's sponsor filed a citizen petition in 2003 requesting that FDA refrain from approving an ANDA for sirolimus with labeling that omitted the protected cyclosporine withdrawal information. In granting the petition, we

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[26] Letter to Gary L. Veron, Esq., Sidley Austin LLP, from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research (May 25, 2011), Docket No. FDA-2010-P-0614.

[27] Letter to Michael S. Labson and Elizabeth M. Walsh, Covington & Burling, from Steven K. Galson, M.D., M.P.H., Acting Director, Center for Drug Evaluation and Research (Sept. 20, 2004), Docket No. 2003P-0518/CP1.

[28] Id. at 1-2. Subsequent to the grant of exclusivity to Rapamune, subparagraph (D) of section 505(c)(3) of the FD&C Act was redesignated as subparagraph (E) by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003. Thus, the relevant exclusivity provision is now located at section 505(c)(3)(E)(iv) of the FD&C Act.

determined that the protected information in the labeling was necessary for safe use, even in the remaining unprotected population (i.e., patients at high risk of immune system reactions) because high-risk patients may be reclassified as low-to-moderate risk and could benefit from information regarding the cyclosporine-sparing regimen.

Here, by contrast, the Agency has concluded that the protected information in Remodulin's labeling regarding the administration of IV treprostinil with a high pH glycine diluent is not necessary for safe use of treprostinil injection. Furthermore, as discussed above, and contrary to the situation in the Rapamune case, FDA lacks reliable evidence from an adequate and well-controlled study that patients will be put at risk if a generic treprostinil injection product is permitted to enter the market with labeling that omits the protected information about high pH glycine diluents.

III. CONCLUSION

For the reasons discussed in this response, your petition is denied. FDA will not refrain from approving an ANDA for treprostinil injection on the basis that it includes proposed labeling that omits the protected information in Remodulin's labeling about how the administration of IV treprostinil with a high pH glycine diluent has been associated with a lower incidence of BSIs compared to neutral diluents when used along with catheter care guidelines. We have concluded that labeling changes necessary to accommodate carve-outs of this information can be made and will not render a generic treprostinil injection product less safe or effective than Remodulin for the treatment of PAH.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research