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BY HAND DELIVERY

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Request for FDA to Refrain from Approving Abbreviated New Drug Applications for Treprostinil that Omit Critical Safety Information in the Labeling

Dear Sir or Madam:

CITIZEN PETITION

United Therapeutics Corp. ("UT") submits this petition pursuant to section 505 of the Federal Food, Drug, and Cosmetic Act ("FDC Act"), among other provisions of law, and 21 C.F.R. §10.30. UT, through this petition, respectfully requests that the Food and Drug Administration ("FDA") refrain from approving any abbreviated new drug application ("ANDA") for treprostinil that omits critical safety information in the approved labeling for Remodulin® (treprostinil) Injection on the administration of intravenous ("IV") treprostinil with a high pH glycine diluent. Administration of IV treprostinil with a high pH glycine diluent has been associated with a lower incidence of bloodstream infections ("BSIs") when used along with central venous catheter care guidelines. This critically important safety information, which currently appears in the labeling of Remodulin, the innovator product, is protected by patent and should not be permitted to be carved out of the labeling for an ANDA submitted for IV treprostinil. Permitting this information to be carved out will render the generic products deficient in important safety information and put patients at risk and, therefore, is not in the interest of public health.

As discussed in more detail below, Remodulin is a prostacyclin analogue approved for the treatment of pulmonary arterial hypertension ("PAH") to diminish symptoms associated with exercise. In light of in vitro studies conducted by UT and information generated through studies of patients, the Remodulin labeling was recently revised to contain information pertaining to the administration of IV Remodulin with a high pH glycine diluent such as Sterile Diluent for Flolan or Sterile Diluent for Epoprostenol Sodium that has been associated with a lower incidence of BSIs when used along with

central venous catheter care guidelines. Omission of this critical information would render a treprostinil product intended for the same conditions of use as Remodulin less safe, and the Agency should accordingly refrain from approving any ANDA for treprostinil that omits such information from the labeling.

UT believes that ANDA applicants, including Sandoz Inc., may submit section viii statements as to a patent held by UT that includes claims protecting administration of Remodulin with a high pH glycine diluent such as Sterile Diluent for Flolan or Sterile Diluent for Epoprostenol Sodium for reducing the risk of BSIs, and attempt to carve this safety information out of their labeling in order to avoid infringing UT's patent. The approval of a treprostinil ANDA with labeling that omits this important safety information would deprive physicians and patients of critical information regarding risks and safe administration of the product and would expose patients to an unreasonably increased risk of potentially fatal BSIs.

A. ACTION REQUESTED

UT requests that FDA refrain from approving any ANDA for treprostinil that does not contain the safety information found in Remodulin labeling pertaining to the administration of IV treprostinil with the specified high pH glycine diluents and the associated lower incidence of BSIs.

B. STATEMENT OF GROUNDS

1. Background

UT is the holder of the approved NDA for Remodulin® (treprostinil) Injection. Remodulin is a prostacyclin analog approved for the treatment of PAH to diminish symptoms associated with exercise. Remodulin can be administered as a continuous subcutaneous infusion or a continuous IV infusion via a central venous catheter. The Orange Book lists four patents for Remodulin. One of these patents, U.S. Patent No. 7,999,007 (the "'007 patent"), claims, *inter alia*, the drug product and a particular use of Remodulin. The use code for the '007 patent, U-1437, contains the following descriptor: "ADMINISTRATION OF REMODULIN DILUTED FOR INTRAVENOUS INFUSION WITH STERILE DILUENT FOR FLOLAN OR STERILE DILUENT FOR EPOPROSTENOL SODIUM PRIOR TO ADMINISTRATION." The '007 patent expires on March 29, 2029.

PAH (WHO Group 1) is a serious, complex, often fatal illness. It is a rare disease, affecting fewer than 200,000 people in the United States. It is characterized by remodeling of the small-to-medium pulmonary arteries, leading to restricted blood flow

and increased pulmonary vascular resistance.[1] Increases in pulmonary vascular resistance cause morphologic and functional changes in the right ventricle. Unlike the left ventricle, the right ventricle cannot sustain long-term increases in pressure. Right ventricle failure is the primary cause of death in patients with PAH. One class of drugs with proven efficacy in reducing ventricular pressure is the prostanoids, including Remodulin and Flolan® (epoprostenol sodium) for Injection.

Flolan, which was originally approved in 1995, is administered as a continuous IV infusion through an indwelling central venous catheter and is required to be reconstituted using only Sterile Diluent for Flolan, which has a basic pH. When Remodulin was originally approved by FDA in 2002, the route of administration was limited to subcutaneous administration. In 2004, FDA approved a supplement to add the IV infusion route of administration to the labeling. Like Flolan, IV Remodulin is administered through an indwelling central venous catheter. Use of such catheters is associated with a risk of complications, including infections such as BSIs. Catheter-related BSIs are "of particular concern because of the risk of severe complications, including endocarditis, lung or brain abscess, osteomyelitis and septic thrombophlebitis."[2] Based on limited clinical experience with IV administration of Remodulin at the time the supplement was approved, the *Adverse Reactions* section of the labeling was revised to mention adverse events related to the drug delivery system: "There are no controlled clinical studies with Remodulin administered intravenously. Among the subjects (n=38) treated for 12 weeks in an open-label study, 2 patients had either line infections or sepsis."[3] At the time, Remodulin was approved for dilution with either Sterile Water for Injection or 0.9% Sodium Chloride Injection, each of which has a neutral pH.[4]

In the years following approval of Remodulin for IV administration, more information became known about the potential for BSIs associated with the use of central venous catheters used for IV prostanoids. In addition, the Centers for Disease Control and Prevention ("CDC") conducted a retrospective investigation to "determine the

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1 *See* M. Humbert, et al., *Pulmonary Arterial Hypertension in France: Results from a National Registry*, 173:9 Am. J. Respir. Crit. Care Med. 1023-1030 (2006) (attached as Exhibit A); V.V. McLaughlin, et al., *ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension: A Report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: Developed in Collaboration with the American College of Chest Physicians, American Thoracic Society, and the Pulmonary Hypertension Association,* 53:17 J. Am. Coll. Cardiol. 1573-619 (2009) (attached as Exhibit B).

2 D. Zaccardelli, 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) (attached as Exhibit C).

3 Remodulin Prescribing Information, at 8 (rev. Nov. 2004), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/021272Orig1s002.pdf ("Remodulin 2004 Prescribing Information").

4 *See id.*, *Dosage and Administration*, at 9.

relative rates of BSI in a sample of patients treated with IV treprostinil and IV epoprostenol during 2003-2006."[5] The published report of the investigation indicated that "based on combined data from seven separate PAH treatment centers, pooled mean rates of BSI (primarily gram-negative BSI) were significantly higher for patients on treprostinil than for those on epoprostenol."[6] The report stated that the results did "not suggest intrinsic contamination of IV treprostinil as a cause of the infections" and hypothesized about possible reasons for the difference in rates.[7]

In February 2008, UT revised the Remodulin labeling in light of the additional information about BSIs collected in the open-label study of treprostinil and the CDC 7-site survey. Among the revisions to the labeling were changes to the *Indications and Usage* section, the *Warnings* section, and the *Adverse Reactions* section.[8] The *Indications and Usage* section was revised to state that "because of the risks associated with chronic indwelling central venous catheters, including serious blood stream infections, continuous intravenous infusion should be reserved for patients who are intolerant of the subcutaneous route, or in whom these risks are considered warranted."[9] The *Warnings* section was revised to state that "chronic intravenous infusions of Remodulin are delivered using an indwelling central venous catheter. This route is associated with the risk of blood stream infections (BSIs) and sepsis, which may be fatal."[10] The *Warnings* section also described the results of the open-label study and the CDC survey: "In an open-label study of IV treprostinil (n=47), there were seven catheter-related line infections during approximately 35 patient years, or about 1 BSI event per 5 years of use. A CDC survey of seven sites that used IV treprostinil for the treatment of PAH found approximately 1 BSI (defined as any positive blood culture) event per 3 years of use."[11]

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5 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) (attached as Exhibit D).

6 *Id.*

7 *Id. See also* A.J. Kallen, et al., *Blood Stream Infections in Patients Given Treatment with Intravenous Prostanoids*, 29:4 Infect. Control Hosp. Epidemiol. 345, 342-9 (Apr. 2008) (in a retrospective review of data from 2 centers, finding higher rates of BSIs and gram-negative BSIs among patients who received treatment with IV prostanoids (treprostinil and epoprostenol) than previously reported among patients who received treatment with IV epoprostenol, with most of the increase "appear[ing] to be the result of higher rates of gram-negative BSI among patients given treatment with [IV] treprostinil") (attached as Exhibit E).

8 *See* Remodulin Prescribing Information (rev. Feb. 2008), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021272s009lbl.pdf ("Remodulin 2008 Prescribing Information").

9 *Id.*, § 1.1.

10 *Id.*, § 5.1.

11 *Id.*

There have been a number of hypotheses regarding the reason for the difference in BSI rates between IV treprostinil and IV epoprostenol.[12] One hypothesis that has been put forward and studied is that the alkaline (or basic) pH of epoprostenol in Sterile Diluent for Flolan has enhanced antimicrobial activity compared with the neutral pH of other common diluents such as sterile saline or water for injection, which have been used for administration with IV treprostinil. In a published report of a study of the stability and antimicrobial activity of treprostinil diluted with Sterile Diluent for Flolan, the results "demonstrate[d] that the antimicrobial effectiveness of treprostinil in [Sterile Diluent for Flolan], which met USP [antimicrobial effectiveness test] standards, is superior to that previously reported for treprostinil in sterile saline for gram-negative and gram-positive bacteria."[13] The study results also demonstrated an anti-bacterial effect for treprostinil in Sterile Diluent for Flolan, which was apparent within 24 to 48 hours after inoculation, particularly with regard to the gram-negative bacteria, *P. aeruginosa* and *E. coli*.[14] This anti-bacterial effect was viewed as potentially important for clinical use of IV treprostinil because patients replace their drug solution every 48 hours.[15] The report also discussed the importance of proper catheter care in preventing catheter-related infections.[16] As a result of demonstrated stability of treprostinil in Flolan Sterile Diluent and the noted antibacterial properties, in September 2008, the Remodulin labeling was revised to add Flolan Sterile Diluent for Injection as an acceptable diluent for IV administration of Remodulin.[17]

In response to the growing body of information regarding an increased frequency of gram-negative infections in patients receiving IV treprostinil, which had been traditionally mixed in a pH-neutral diluent, a study was performed to test the hypothesis that administering IV treprostinil with epoprostenol diluent, which has a basic pH, would result in a lower incidence of gram-negative BSIs.[18] The results of this prospective study, which were recently published, were as follows:

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12 *See, e.g.*, Kallen, *supra* note 7, at 346-7 (describing potential reasons for the difference as preparation and storage of the medications; a potential increased willingness of patients receiving treprostinil to detach the IV catheter in light of the longer half life of treprostinil; and the possibility that prostanoids may have anti-inflammatory effects. Leading to speculations that there may be different levels of immunomodulatory activity between the products); CDC, *supra* note 5, at 171-2 (describing same hypotheses).

13 Zaccardelli, *supra* note 2, at 889.

14 *Id.* (describing a $\log_{10}$ reduction of >4 for treprostinil in Sterile Diluent for Flolan compared with no reduction of growth of these same organisms in treprostinil in sterile saline).

15 *Id.*

16 *Id.*

17 *See* Remodulin 2008 Prescribing Information, §§ 2.1, 2.6, and 16.

18 *See* J.D. Rich, 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) (attached as Exhibit F).

- Significantly fewer gram-negative BSIs in those treated with IV treprostinil in epoprostenol diluent compared to those treated with IV treprostinil in native (pH neutral) diluent (0.08 of 1,000 treatment days vs. 0.71 of 1,000 treatment days; p=0.01)
- A strong trend toward lower overall BSI rates among those treated with IV treprostinil in epoprostenol diluent compared to those treated with IV treprostinil in native diluent (0.32 of 1,000 treatment days vs. 0.90 of 1,000 treatment days; p=0.06)
- Lower, but not statistically significant, differences in BSI rates in those patients treated with IV treprostinil in epoprostenol diluent compared with those treated with epoprostenol (0.32 of 1,000 treatment days vs. 0.40 of 1,000 treatment days; p=0.79)[19]

The article concluded that, "[b]ecause our findings are consistent with the in vitro data of a significant reduction in gram-negative infections with the use of treprostinil in epoprostenol diluent, the dilution of treprostinil with epoprostenol diluent is highly recommended."[20] The article also mentioned the importance of adherence to appropriate catheter care guidelines.

Based on this new information, FDA agreed that Remodulin labeling should be revised to include additional information pertaining to the risk of BSIs in the administration of IV Remodulin. Specifically, in September 2013, FDA approved revisions to the *Warnings and Precautions* section of the labeling stating: "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."[21]

At least one ANDA sponsor, Sandoz, has publicly represented that it will seek to omit from its proposed generic labeling use of treprostinil with a high pH glycine diluent. Hence, UT is submitting this citizen petition.

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19 *Id.* at 38.

20 *Id.* at 40.

21 *See* Remodulin Prescribing Information, § 5.1 (rev. Sept. 2013), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021272s020lbledt.pdf ("Remodulin 2013 Prescribing Information").

2. Analysis

a. Omission of Safety Information Regarding Reduction of BSI Risk Would Render Generic Treprostinil Products Less Safe than Remodulin for the Remaining, Non-protected Conditions of Use.

As discussed above, UT's '007 patent protects administration of Remodulin with a high pH glycine diluent such as Sterile Diluent for Flolan or Sterile Diluent for Epoprostenol Sodium for reducing the risk of BSIs, which means that the labeling for a generic treprostinil product cannot contain such information until the patent expires. The question then becomes whether the labeling for a generic treprostinil product that omits the protected information could be approved. Labeling of treprostinil products intended for the same conditions of use as Remodulin that omits reference to the use of IV treprostinil with a high pH glycine diluent to reduce the risk of BSIs would render the products less safe than Remodulin and unapprovable under section 505 of the FDC Act.

The FDC 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]" and "information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug . . ."[22] The FDC Act provides the following two exceptions for when ANDA labeling may differ from that of the listed drug: (1) when changes reflect differences approved pursuant to an ANDA suitability petition or (2) when the drugs are produced or distributed by different manufacturers.[23] FDA regulations implementing the statutory exceptions to the ANDA labeling requirement state that "differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include . . . omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the [FDC Act]."[24] The regulations further provide that to approve an ANDA that omits an aspect of labeling protected by patent or exclusivity, FDA must find that the "differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use."[25] In the preamble to the final rule, FDA explains that "it will not

22 21 U.S.C. § 355(j)(2)(A)(i), (v).

23 *Id.* § 355(j)(2)(A)(v).

24 21 C.F.R. § 314.94(a)(8)(iv).

25 *Id.* § 314.127(a)(7). UT does not challenge FDA's general authority to permit "carve-outs" of protected information in certain circumstances, authority that has been recognized in court decisions. *See, e.g., Sigma-Tau Pharmaceuticals, Inc. v. Schwetz*, 288 F.3d 141 (4th Cir. 2002); *Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493 (D.C. Cir. 1996). Rather, UT asserts, as described in more detail below, that carving out the safety information is inappropriate because it does not meet the requirements of 21 C.F.R. § 314.124(a)(7).

approve an ANDA with different labeling if the labeling differences affect product safety or efficacy."[26]

The FDC Act and FDA's implementing regulations thus do not permit FDA to approve an ANDA for treprostinil that does not contain the information related to administration of IV treprostinil with a high pH glycine diluent because, as discussed in detail below, such omission would render generic treprostinil less safe than Remodulin for its non-protected conditions of use.

As discussed above, use of indwelling central venous catheters is associated with a risk of complications, including infections such as BSIs. Catheter-related BSIs are "of particular concern because of the risk of severe complications, including life-threatening endocarditis, lung or brain abscess, osteomyelitis and septic thrombophlebitis."[27] Reports of BSIs with the use of IV Remodulin has led to a significant amount of investigation and research into the frequency and potential cause. In light of the information learned by the CDC, UT, and other investigators regarding BSIs and IV treprostinil, UT recently sought and received approval from FDA to revise the Remodulin labeling to include additional information pertaining to the risk of BSIs in the administration of IV Remodulin. As discussed above, the *Warnings and Precautions* section of the labeling were revised to include the following patent-protected information: "[a]dministration 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."[28]

Information that is placed in the *Warnings and Precautions* section of the treprostinil labeling and that informs a prescriber of IV treprostinil that a high pH diluent such as Sterile Diluent for Flolan or Sterile Diluent for Epoprostenol Sodium has been associated with a lower incidence of BSIs is critical to have when prescribing the drug. Without that information, a prescriber or patient may not be aware that he or she could reduce the potential for a patient to acquire a serious and potentially life-threatening infection such as a BSI through the choice of diluent.

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26 57 Fed. Reg. 17,950, 17,968 (Apr. 28, 1992).

27 Zaccardelli, *supra* note 2, at 885.

28 Remodulin 2013 Prescribing Information, § 5.1.

b. FDA Has Consistently Determined that ANDAs Cannot Be Approved with Labeling Carve-Outs of Essential Safety Information.

Based on the aforementioned statutory and regulatory provisions, FDA has granted petitions requesting relief similar to that requested by UT in this petition. Most recently, in 2011, FDA granted a portion of the petition submitted by Mutual Pharmaceutical Company ("Mutual") requesting that FDA not allow any applicants referencing Colcrys® (colchicine, USP) Tablets to carve out protected information pertaining to acute gout flares and the risk of toxicity if the use of colchicine for prophylaxis of gout flares is not coordinated with treatment of an acute gout flare.[29] Since Mutual had received three years of marketing exclusivity for the treatment of acute gout flares, FDA reasoned that it was appropriate to consider "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."[30] FDA concluded that "[t]o the extent that a healthcare provider determines it is necessary to use colchicine for treatment of an acute gout flare in a patient receiving colchicine for prophylaxis, adequate information about potential toxicity of colchicine dosing would be important to minimize risk of cumulative toxicity" and the labeling should inform healthcare providers that a lower dose regimen is adequate to treat an acute gout flare.[31]

The same is true for treprostinil. For prescribers who determine that it is necessary to prescribe IV treprostinil for patients who are intolerant of the subcutaneous route, or in whom these risks are considered warranted, adequate information about a potential method to reduce the risk of a patient acquiring a BSI is crucial and must be provided in the labeling. If such information is omitted, the drug is less safe for IV treprostinil use.

Similarly, FDA granted the petition submitted by Wyeth Pharmaceuticals ("Wyeth") requesting that FDA refrain from approving any generic versions of Rapamune® (sirolimus) Tablets that omitted critical information pertaining to cyclosporine before the expiration date of statutory exclusivity for protected information.[32] In that case, FDA concluded that the omission of information pertaining to a cyclosporine withdrawal clinical study contained in the labeling would render the

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29 *See* Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, to Gary L. Veron, Esq., Sidley Austin, LLP, Docket No. FDA-2010-P-0614, at 21-24 (May 25, 2011).

30 *Id.* at 24.

31 *Id.*

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

product less safe for the remaining, non-protected conditions of use. FDA noted that the protected labeling "contains extensive, critical prescribing information pertaining to cyclosporine withdrawal that any physician should receive to appropriately determine treatment for all indications of sirolimus."[33]

Again, the same is true for treprostinil. As discussed above, patients using IV Remodulin do so through an indwelling central venous catheter. Consistent with FDA's conclusions with respect to Rapamune, omitting information from a generic treprostinil's labeling relating to use with a high pH glycine diluent that is associated with lower incidence of BSIs would render the generic product less safe than the innovator product.

A review of recent FDA determinations permitting ANDA or 505(b)(2) applicants to carve out certain protected information in order to obtain approval for those products demonstrates why omitting the protected information in this case would render generic treprostinil less safe for the remaining conditions of use. Most of the decisions permitting carve outs pertain to situations in which there is an indication and, at times, related information that is protected by patent or marketing exclusivity.[34] In such cases, it is easier to argue that omission of a distinct indication does not render a drug less safe or effective for the remaining non-protected conditions of use because the protected information often is unrelated and more easily segregated and does not affect the other uses. Here, however, the safety information regarding reducing the risk of BSIs is applicable to *any* IV use of treprostinil for the *only* approved indication. Accordingly, the decisions permitting carve outs for indications are inapposite.

c. Conclusion.

For the reasons discussed above, FDA must refrain from approving ANDAs for treprostinil with labeling that does not include the approved safety information regarding administration of treprostinil with a high pH glycine diluent such as Sterile Diluent for Flolan or Sterile Diluent for Epoprostenol Sodium. The removal of such information

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33 *Id.* at 3.

34 *See, e.g.*, Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, to Robert Trainer, Executive Vice President and General Counsel, UCB, Inc., Docket No: FDA-2010-P-0545 (Feb. 24, 2011) (permitting ANDA labeling for a levocetirizine dihydrochloride product to carve out allergic rhinitis indications for which Xyzal is approved); Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, to Stephen R. Auten, Esq., Vice President, Legal-Intellectual Property, Sandoz, Inc., Docket No. FDA-2010-P-0087 (Aug. 3, 2010) (permitting ANDA labeling for a pregabalin product to carve out either the seizure indication or the pain-related indications for which Lyrica is approved).

from labeling would deny physicians and patients critical information and expose patients to unreasonable risks of BSI.

C. ENVIRONMENTAL IMPACT

A claim for categorical exclusion from the requirements for an Environmental Assessment is made under 21 C.F.R. § 25.31(a).

D. ECONOMIC IMPACT

An economic impact statement will be submitted at the request of the Commissioner.

E. CERTIFICATION

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: September 26, 2013. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: my employer, United Therapeutics Corp., in the regular course of my employment. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,

Dean Bunce
Executive Vice President
Regulatory Affairs and Compliance
United Therapeutics Corp.

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