CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-387

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-387

NDA APPROVAL

United Therapeutics Corporation
Attention: Mr. Dean Bunce
P.O. Box 14186
55 TW Alexander Drive
Research Triangle Park, NC 27709

Dear Mr. Bunce:

Please refer to your June 27, 2008 new drug application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Tyvaso (treprostinil) Inhalation Solution.

We acknowledge receipt of your submissions dated July 3, August 14 and 26, September 26, October 1, 9, 24, 29, and 31, November 12 and 13, and December 22, 2008, and January 2, 22, and 29, February 9, 19, and 25, March 12, April 1 (two), 3 (two), 8, 16, 17, 24, and 29, May 7, June 5, 17, and 25 (two), July 2, 7, 9, 22, and 28, 2009.

This new drug application provides for the use of Tyvaso for the treatment of pulmonary arterial hypertension (WHO Group I) in patients with NYHA Class III symptoms, to increase walk distance.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm that is identical to the enclosed agreed-upon labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 22-387**."

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22-387.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PROPRIETARY NAME

The Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Cardiovascular and Renal Products do not object to the use of the proprietary name, Tyvaso, for this product.

PEDIATRIC RESEARCH EQUITY ACT (PREA)

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have sufficient concerns that treprostinil by the inhaled route of administration may be irritating to the respiratory tract. This concern is based on:

- Adverse events observed during the clinical experience
- Observations of oropharyngeal and other respiratory tract lesions in rats and dogs during the preclinical assessments of inhaled treprostinil
- The finding that when administered by the subcutaneous route, treprostinil is extremely irritating at the site of administration.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of oropharyngeal or pulmonary toxicity in patients using Tyvaso (treprostinil).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1. A long-term observational study in the US that will include another 1000 patient-years of follow-up in Tyvaso-treated patients, and 1000 patient-years of follow-up in matched controls receiving other treatments for pulmonary hypertension, to evaluate the potential association between Tyvaso (treprostinil) and oropharyngeal and pulmonary toxicity.

The timetable you submitted on July 28, 2009 states that you will conduct this study according to the following timetable:

Draft Protocol Submission:	September 15, 2009
Final Protocol Submission:	December 15, 2009
Interim Study Report #1:	December 31, 2011
Interim Study Report #2:	September 30, 2012
Study Completion Date:	June 30, 2013
Final Report Submission/Supplement:	December 15, 2013

Submit the protocol to your IND, with a cross-reference letter to NDA 22-387. Submit all final report(s) to NDA 22-387. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to

submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS OF 21 CFR 314.81

We remind you of your postmarketing commitment in your submission dated July 28, 2009. You commit to:

2. Re-engineer the Optineb-IR device including the following changes: create a titratable breath counter, align/key the dome of the device, add a battery back-up power pack, and permanently fix the baffle plate to the dome.

Final Protocol Submission:	October 1, 2009
Study Completion Date:	February 28, 2010
Final Report Submission:	March 31, 2010
Submit Supplement:	October 31, 2010

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS OF 21 CFR 314.81

3. As part of the re-engineering described in PMC number 2, you should perform a usability analysis incorporating the evaluation and prioritization of user-related risk followed by a human factors analysis.

Final Protocol Submission:	October 1, 2009
Study Completion Date:	February 28, 2010
Final Report Submission:	March 31, 2010
Submit Supplement:	October 31, 2010

4. Conduct a study to collect pharmacokinetic data to verify expected dosing with the new Optineb-IR device.

Final Protocol Submission:	December 1, 2009
Final Report Submission:	August 30, 2010
Submit Supplement:	October 31, 2010

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments should

be prominently labeled "**Postmarketing Commitment Protocol,**" "**Postmarketing Commitment Final Report,**" or "**Postmarketing Commitment Correspondence.**"

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Dan Brum, Pharm.D., MBA, RAC, Regulatory Project Manager, at (301) 796-0578.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure: Agreed-upon labeling