DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-272

United Therapeutics Corporation
Attention: Mr. Dean Bunce
68 T.W. Alexander Drive
Research Triangle Park, N.C. 27709

Dear Mr. Bunce:

Please refer to your new drug application (NDA) dated October 16, 2000, withdrawn July 5, 2001 and resubmitted on August 9, 2001. This application was submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Remodulin (treprostinil sodium) Injection, 1.0, 2.5, 5.0, and 10.0 mg/ml.

We acknowledge receipt of your submissions dated February 12, 13, 20 (two), 25, and 28, March 14 and 20 (two), April 1 and 2, and May 8, 2002. Your submission of April 1, 2002 constituted a complete response to our February 8, 2002 approvable letter.

This new drug application provides for the use of Remodulin (treprostinil sodium) Injection 1.0, 2.5, 5.0, and 10.0 mg/ml for the treatment of pulmonary arterial hypertension (PAH).

We have completed the review of this application, as amended, according to the regulations for accelerated approval, and have concluded that adequate information has been presented to approve Remodulin (treprostinil sodium) Injection 1.0, 2.5, 5.0, and 10.0 mg/ml for use as recommended in the final printed labeling (package insert and immediate container and carton labels included in your submission of March 21, 2002). Accordingly, the application is approved under Subpart H of the Code of Federal Regulations (21 CFR 314.510). Approval is effective on the date of this letter. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of the referenced accelerated approval regulations.

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies to verify and describe clinical benefit. We remind you of your post marketing study (Subpart H post marketing commitments) specified in your submission dated April 1, 2002. These commitments, along with any completion dates agreed upon, are listed below.

We note your submission of April 1, 2002, in which you committed to the performance of a clinical study, P01:13 as outlined in your amendment dated April 1, 2002. This study is titled "*A multicenter, randomized, parallel placebo-controlled study of the safety and efficacy of subcutaneous Remodulin™ therapy after transition from Flolan® in patients with pulmonary arterial hypertension.*" In this study a total of approximately 100 patients who are clinically stable on regimens for their pulmonary hypertension are to be withdrawn from Flolan and randomized to receive either placebo or Remodulin. The primary endpoint of the study is the time to clinical deterioration defined as the time from

initiation of study drug to earliest incidence of clinical worsening of PAH symptoms requiring reinstitution of Flolan therapy, to rehospitalization, or to death. As patients will be closely monitored, deaths are not expected. The study is powered based on the expected occurrence of at least 50 events.

The time-lines for completion of P01:13 (and affirmed in your April 2, 2002 submission) are as follows:

50% of Planned Enrollment:	by June 2, 2003
Full (100%) Enrollment:	by December 2, 2003
Submission of Complete Study Report:	by June 2, 2004

Please note that failure to adhere to these time lines may be considered a failure to show due diligence (21 CFR 314.510) and may trigger Agency action to withdraw marketing approval under 21 CFR 314.530.

The final study report should be submitted to this NDA as part of a supplemental application. For administrative purposes, all submissions relating to this post marketing commitment must be clearly designated "Subpart H Post Marketing Commitments."

We also remind you that, under 21 CFR 314.550, after the initial 120 day period following this approval, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please be note that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred as described in the Federal Register notice of December 2, 1998 (63 *FR* 66632). We acknowledge your request of October 16, 2000 asking for a waiver of the pediatric study requirement for this action on this application. In accordance with 21 CFR 314.55(d), we agree to waive that requirement for this application for all pediatric study groups covered by the Pediatric Rule.

In a telephone conversation with Mr. Edward Fromm, Division of Cardio-Renal Drug Products, on May 14, 2002, you agreed to make the following changes to the package insert at the time of your next printing:

1) Under **PRECAUTIONS, Hepatic and Renal Impairment**, the phrase "**SPECIAL POPULATIONS**" should not be capitalized and should be changed to "**Special Populations**".

2) Under **HOW SUPPLIED**, the sentence that reads "Unopened vials of Remodulin are stable until the date indicated when stored at 15 to 25°C (59 to 77°F)" should be deleted.

Please report these changes in your first annual report.

In addition, under **Clinical Trials in Pulmonary Arterial Hypertension** and **Adverse Reactions**, please add a discussion of whether differences were seen in demographic subgroups. This information should be submitted as a prior approval supplemental application.

We also note that there were minor editorial changes made throughout the package insert.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Mr. Edward Fromm
Regulatory Health Project Manager
(301) 594-5313

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Temple
5/21/02 06:01:00 PM