DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20-845/S-009 **APPROVAL LETTER**

INO Therapeutics, Inc.
Attention: Mary Ellen Zamstein
Senior Director, Regulatory Affairs
6 State Route 173
Clinton, NJ 08809

Dear Ms. Zamstein:

Please refer to your supplemental new drug application dated February 25, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for INOmax (nitric oxide) for Inhalation.

This supplemental new drug application provides for labeling revised as follows:

1. The label has been converted to the new PLR format.

2. The following text, which was originally under the DOSAGE AND ADMINISTRATION section, has been moved to the INDICATIONS AND USAGE section (this applies to both the FPI, and Highlights, where appropriate):

   Utilize additional therapies to maximize oxygen delivery. In patients with collapsed alveoli, additional therapies might include surfactant and high-frequency oscillatory ventilation.

   The safety and effectiveness of inhaled nitric oxide have been established in a population receiving other therapies for hypoxic respiratory failure, including vasodilators, intravenous fluids, bicarbonate therapy, and mechanical ventilation. Different dose regimens for nitric oxide were used in the clinical studies *[see Clinical Studies (14)]*.

   Monitor for PaO_2, methemoglobin, and inspired NO_2 during INOmax administration.

3. The following new warning for use in patients with pre-existing left-ventricular dysfunction has been added to the appropriate sections of the label:

   Highlights/RECENT MAJOR CHANGES:
   Warnings and Precautions, Heart Failure (5.4) 8/2009

   Highlights/WARNINGS AND PRECAUTIONS:
   Heart Failure: In patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase pulmonary capillary wedge pressure leading to pulmonary edema (5.4).

   Full Prescribing Information/WARNINGS AND PRECAUTIONS:
   5.4 Heart Failure
   Patients who had pre-existing left ventricular dysfunction treated with inhaled nitric oxide, even for short durations, experienced serious adverse events (e.g., pulmonary edema).

4. The first sentence of the OVERDOSAGE section has been changed from:

   Overdosage with INOmax will be manifest by elevations in methemoglobin and NO_2.

   To:

   Overdosage with INOmax will be manifest by elevations in methemoglobin and pulmonary toxicities associated with inspired NO_2.

5. Under CLINICAL PHARMACOLOGY/Mechanism of Action, the following sentence has been added to the end of the first paragraph:

   When inhaled, nitric oxide selectively dilates the pulmonary vasculature, and because of efficient scavenging by hemoglobin, has minimal effect on the systemic vasculature.

6. Under CLINICAL STUDIES, the title of the subsection on ARDS has been changed from:

   Other Clinical Data: Adult Respiratory Distress Syndrome (ARDS)

   To:

   Ineffective in Adult Respiratory Distress Syndrome (ARDS)

7. The revision date has been updated.

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

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/oc/datacouncil/spl.html that is identical to the enclosed labeling. 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 20-845/S-009." Approval of this submission by FDA is not required before the labeling is used.

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

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

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 call Mr. Russell Fortney, Regulatory Project Manager, at (301) 796-1068.

Sincerely,

{See appended electronic signature page}

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

Enclosure: Agreed-upon labeling text

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

/s/

NORMAN L STOCKBRIDGE
08/26/2009