

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

*APPLICATION NUMBER:*

**NDA 20845/ S17**

*Trade Name:* **INOMAX**

*Generic Name:* **Nitric Oxide**

*Sponsor:* **Mallinckrodt Hospital**

*Approval Date:* 10/09/2015

*Indications:* INOmax is a vasodilator indicated to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilatory support and other appropriate agents.

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*  
**NDA 20845/S17**

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***  
**NDA 20845/S17**

**APPROVAL LETTER**



NDA 20845/S-016, S-017

## SUPPLEMENT APPROVAL

Mallinckrodt Hospital Products IP Limited  
c/o: INO Therapeutics  
Attention: Mary Ellen Anderson  
Senior Director, Regulatory Affairs  
Perryville III Corporate Park  
53 Frontage Road, Third Floor, Box 9001  
Hampton, NJ 08827

Dear Ms. Anderson:

Please refer to your Supplemental New Drug Applications (sNDAs) dated December 8, 2014 (S-016) and December 11, 2014 (S-017) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for INOmax (nitric oxide) for inhalation.

We acknowledge receipt of your amendments dated August 27, 2015 (S-016) and January 30 and February 13, 2015 (S-017).

The August 27, 2015 submission constituted a complete response to our June 4, 2015 action letter for S-016.

These "Prior Approval" supplemental new drug applications propose the following:

### **S-016**

The removal of the 100 ppm nitric oxide concentration from the labeling and revisions to the **DOSAGE AND ADMINISTRATION** and **WARNINGS AND PRECAUTIONS** sections of the INOmax package inserts.

### **S-017**

Revisions to the labeling based on the clinical study entitled "*Bronchopulmonary Dysplasia (BPD) in Preterm Infants Requiring Mechanical Ventilation or Positive Pressure Support on Days 5 to 14 After birth (IK-3001-BPD-301)*".

### **APPROVAL & LABELING**

We have completed our review of these supplemental applications, as amended. They are 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, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending “Changes Being Effectuated” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

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

## **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf> ).

Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf> ).

## **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 Brian Proctor, Regulatory Project Manager, at (240) 402-3596.

Sincerely,

*{See appended electronic signature page}*

Mary Ross Southworth, Pharm.D.  
Deputy Director for Safety  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

ENCLOSURE(S):  
Content of Labeling

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARY R SOUTHWORTH  
10/09/2015

**CENTER FOR DRUG EVALUATION AND  
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***APPLICATION NUMBER:***  
**NDA 20845/S17**

**LABELING**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use INOMAX safely and effectively. See full prescribing information for INOMAX.

**INOMAX (nitric oxide) gas, for inhalation**  
Initial U.S. Approval: 1999

-----**RECENT MAJOR CHANGES**-----  
Dosage and Administration (2.2) 10/2015

-----**INDICATIONS AND USAGE**-----  
INOMax is a vasodilator indicated to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilatory support and other appropriate agents.

-----**DOSAGE AND ADMINISTRATION**-----  
The recommended dose is 20 ppm, maintained for up to 14 days or until the underlying oxygen desaturation has resolved (2.1).  
Doses greater than 20 ppm are not recommended (2.1, 5.2)  
Administration:

- Use only with an INOMax DS<sub>IR</sub><sup>®</sup> operated by trained personnel (2.2)
- Avoid abrupt discontinuation (2.2, 5.1).

-----**DOSAGE FORMS AND STRENGTHS**-----

INOMax (nitric oxide) is a gas available in an 800 ppm concentration (3).

-----**CONTRAINDICATIONS**-----  
Neonates dependent on right-to-left shunting of blood (4).

-----**WARNINGS AND PRECAUTIONS**-----  
Rebound: Abrupt discontinuation of INOMax may lead to worsening oxygenation and increasing pulmonary artery pressure (5.1).  
Methemoglobinemia: Methemoglobin increases with the dose of nitric oxide; following discontinuation or reduction of nitric oxide, methemoglobin levels return to baseline over a period of hours (5.2).  
Elevated NO<sub>2</sub> Levels: Monitor NO<sub>2</sub> levels (5.3).  
Heart Failure: In patients with pre-existing left ventricular dysfunction, INOMax may increase pulmonary capillary wedge pressure leading to pulmonary edema (5.4).

-----**ADVERSE REACTIONS**-----  
The most common adverse reaction is hypotension. (6).

**To report SUSPECTED ADVERSE REACTIONS, contact INO Therapeutics at 1-877-566-9466 and <http://www.inomax.com/> or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

-----**DRUG INTERACTIONS**-----  
Nitric oxide donor compounds may increase the risk of developing methemoglobinemia (7).

Revised: 10/2015

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

INOMax<sup>®</sup> is indicated to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilatory support and other appropriate agents.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Dosage

##### Term and near-term neonates with hypoxic respiratory failure

The recommended dose of INOMax is 20 ppm. Maintain treatment up to 14 days or until the underlying oxygen desaturation has resolved and the neonate is ready to be weaned from INOMax therapy.

Doses greater than 20 ppm are not recommended [*see Warnings and Precautions (5.2)*].

#### 2.2 Administration

##### Training in Administration

The user of INOMax and Nitric Oxide Delivery Systems must satisfactorily complete a comprehensive periodic training program for health care professionals provided by the delivery system and drug manufacturers. Health professional staff that administers nitric oxide therapy have access to supplier-provided 24 hour/365 days per year technical support on the delivery and administration of INOMax at 1-877-566-9466.

##### Nitric Oxide Delivery Systems

INOMax must be administered using a calibrated INOMax DS<sub>IR</sub><sup>®</sup> Nitric Oxide Delivery System. Only validated ventilator systems should be used in conjunction with INOMax. Consult the Nitric Oxide Delivery System label or call 877.566.9466/visit inomax.com for a current list of validated systems.

Keep available a backup battery power supply and an independent reserve nitric oxide delivery system to address power and system failures.

##### Monitoring

Measure methemoglobin within 4-8 hours after initiation of treatment with INOMax and periodically throughout treatment [*see Warnings and Precautions (5.2)*].

Monitor for PaO<sub>2</sub> and inspired NO<sub>2</sub> during INOMax administration [*see Warnings and Precautions 5.3*].

##### Weaning and Discontinuation

Avoid abrupt discontinuation of INOmax [see *Warnings and Precautions (5.1)*]. To wean INOmax, downtitrate in several steps, pausing several hours at each step to monitor for hypoxemia.

### **3 DOSAGE FORMS AND STRENGTHS**

INOmax (nitric oxide) gas is available in an 800 ppm concentration.

### **4 CONTRAINDICATIONS**

INOmax is contraindicated in neonates dependent on right-to-left shunting of blood.

### **5 WARNINGS AND PRECAUTIONS**

#### **5.1 Rebound Pulmonary Hypertension Syndrome following Abrupt Discontinuation**

Wean from INOmax [see *Dosage and Administration (2.2)*]. Abrupt discontinuation of INOmax may lead to worsening oxygenation and increasing pulmonary artery pressure, i.e., Rebound Pulmonary Hypertension Syndrome. Signs and symptoms of Rebound Pulmonary Hypertension Syndrome include hypoxemia, systemic hypotension, bradycardia, and decreased cardiac output. If Rebound Pulmonary Hypertension occurs, reinstate INOmax therapy immediately.

#### **5.2 Hypoxemia from Methemoglobinemia**

Nitric oxide combines with hemoglobin to form methemoglobin, which does not transport oxygen. Methemoglobin levels increase with the dose of INOmax; it can take 8 hours or more before steady-state methemoglobin levels are attained. Monitor methemoglobin and adjust the dose of INOmax to optimize oxygenation.

If methemoglobin levels do not resolve with decrease in dose or discontinuation of INOmax, additional therapy may be warranted to treat methemoglobinemia [see *Overdosage (10)*].

#### **5.3 Airway Injury from Nitrogen Dioxide**

Nitrogen dioxide (NO<sub>2</sub>) forms in gas mixtures containing NO and O<sub>2</sub>. Nitrogen dioxide may cause airway inflammation and damage to lung tissues.

If there is an unexpected change in NO<sub>2</sub> concentration, or if the NO<sub>2</sub> concentration reaches 3 ppm when measured in the breathing circuit, then the delivery system should be assessed in accordance with the Nitric Oxide Delivery System O&M Manual troubleshooting section, and the NO<sub>2</sub> analyzer should be recalibrated. The dose of INOmax and/or FiO<sub>2</sub> should be adjusted as appropriate.

#### **5.4 Worsening Heart Failure**

Patients with left ventricular dysfunction treated with INOmax may experience pulmonary edema, increased pulmonary capillary wedge pressure, worsening of left ventricular dysfunction, systemic hypotension, bradycardia and cardiac arrest. Discontinue INOmax while providing symptomatic care.

## **6 ADVERSE REACTIONS**

The following adverse reactions are discussed elsewhere in the label;

Hypoxemia [*see Warnings and Precautions (5.2)*]

Worsening Heart Failure [*see Warnings and Precautions (5.4)*]

### **6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from the clinical studies does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Controlled studies have included 325 patients on INOmax doses of 5 to 80 ppm and 251 patients on placebo. Total mortality in the pooled trials was 11% on placebo and 9% on INOmax, a result adequate to exclude INOmax mortality being more than 40% worse than placebo.

In both the NINOS and CINRGI studies, the duration of hospitalization was similar in INOmax and placebo-treated groups.

From all controlled studies, at least 6 months of follow-up is available for 278 patients who received INOmax and 212 patients who received placebo. Among these patients, there was no evidence of an adverse effect of treatment on the need for rehospitalization, special medical services, pulmonary disease, or neurological sequelae.

In the NINOS study, treatment groups were similar with respect to the incidence and severity of intracranial hemorrhage, Grade IV hemorrhage, periventricular leukomalacia, cerebral infarction, seizures requiring anticonvulsant therapy, pulmonary hemorrhage, or gastrointestinal hemorrhage.

In CINRGI, the only adverse reaction (>2% higher incidence on INOmax than on placebo) was hypotension (14% vs. 11%).

### **6.2 Post-Marketing Experience**

Post marketing reports of accidental exposure to nitric oxide for inhalation in hospital staff has been associated with chest discomfort, dizziness, dry throat, dyspnea, and headache.

## **7 DRUG INTERACTIONS**

### **7.1 Nitric Oxide Donor Agents**

Nitric oxide donor agents such as prilocaine, sodium nitroprusside and nitroglycerine may increase the risk of developing methemoglobinemia.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Pregnancy Category C

Animal reproduction studies have not been conducted with INOmax. It is not known if INOmax can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. INOmax is not indicated for use in adults.

### 8.3 Nursing Mothers

Nitric oxide is not indicated for use in the adult population, including nursing mothers. It is not known whether nitric oxide is excreted in human milk.

### 8.4 Pediatric Use

The safety and efficacy of nitric oxide for inhalation has been demonstrated in term and near-term neonates with hypoxic respiratory failure associated with evidence of pulmonary hypertension [see *Clinical Studies (14.1)*]. Additional studies conducted in premature neonates for the prevention of bronchopulmonary dysplasia have not demonstrated substantial evidence of efficacy [see *Clinical Studies (14.3)*]. No information about its effectiveness in other age populations is available.

### 8.5 Geriatric Use

Nitric oxide is not indicated for use in the adult population.

## 10 OVERDOSAGE

Overdosage with INOmax is manifest by elevations in methemoglobin and pulmonary toxicities associated with inspired NO<sub>2</sub>. Elevated NO<sub>2</sub> may cause acute lung injury. Elevations in methemoglobin reduce the oxygen delivery capacity of the circulation. In clinical studies, NO<sub>2</sub> levels >3 ppm or methemoglobin levels >7% were treated by reducing the dose of, or discontinuing, INOmax.

Methemoglobinemia that does not resolve after reduction or discontinuation of therapy can be treated with intravenous vitamin C, intravenous methylene blue, or blood transfusion, based upon the clinical situation.

## 11 DESCRIPTION

INOmax (nitric oxide gas) is a drug administered by inhalation. Nitric oxide, the active substance in INOmax, is a pulmonary vasodilator. INOmax is a gaseous blend of nitric oxide and nitrogen (0.08% and 99.92%, respectively for 800 ppm). INOmax is supplied in aluminum cylinders as a compressed gas under high pressure (2000 pounds per square inch gauge [psig]).

The structural formula of nitric oxide (NO) is shown below:



## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Nitric oxide relaxes vascular smooth muscle by binding to the heme moiety of cytosolic guanylate cyclase, activating guanylate cyclase and increasing intracellular levels of cyclic guanosine 3',5'-monophosphate, which then leads to vasodilation. When inhaled, nitric oxide selectively dilates the pulmonary vasculature, and because of efficient scavenging by hemoglobin, has minimal effect on the systemic vasculature.

INOMax appears to increase the partial pressure of arterial oxygen ( $\text{PaO}_2$ ) by dilating pulmonary vessels in better ventilated areas of the lung, redistributing pulmonary blood flow away from lung regions with low ventilation/perfusion (V/Q) ratios toward regions with normal ratios.

### 12.2 Pharmacodynamics

#### Effects on Pulmonary Vascular Tone in PPHN

Persistent pulmonary hypertension of the newborn (PPHN) occurs as a primary developmental defect or as a condition secondary to other diseases such as meconium aspiration syndrome (MAS), pneumonia, sepsis, hyaline membrane disease, congenital diaphragmatic hernia (CDH), and pulmonary hypoplasia. In these states, pulmonary vascular resistance (PVR) is high, which results in hypoxemia secondary to right-to-left shunting of blood through the patent ductus arteriosus and foramen ovale. In neonates with PPHN, INOMax improves oxygenation (as indicated by significant increases in  $\text{PaO}_2$ ).

### 12.3 Pharmacokinetics

The pharmacokinetics of nitric oxide has been studied in adults.

#### *Absorption and Distribution*

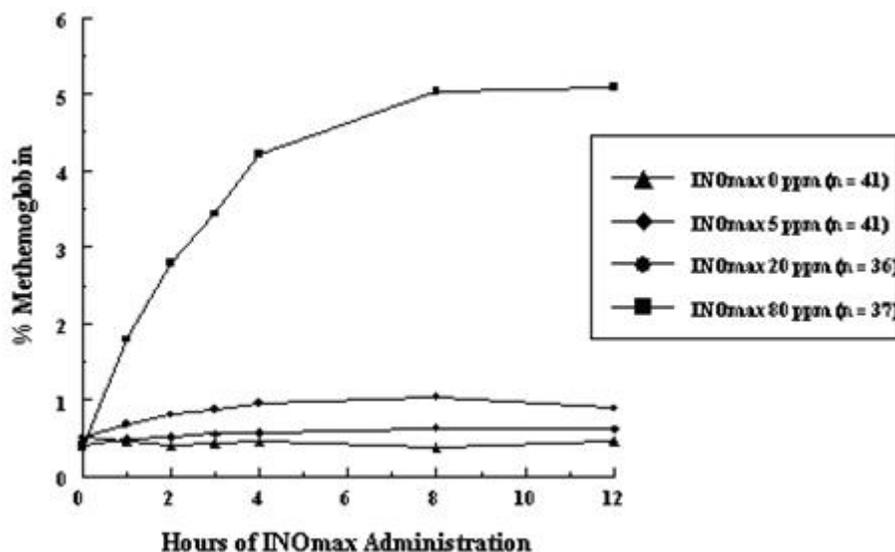
Nitric oxide is absorbed systemically after inhalation. Most of it traverses the pulmonary capillary bed where it combines with hemoglobin that is 60% to 100% oxygen-saturated. At this level of oxygen saturation, nitric oxide combines predominantly with oxyhemoglobin to produce methemoglobin and nitrate. At low oxygen saturation, nitric oxide can combine with deoxyhemoglobin to transiently form nitrosylhemoglobin, which is converted to nitrogen oxides and methemoglobin upon exposure to oxygen. Within the pulmonary system, nitric oxide can combine with oxygen and water to produce nitrogen dioxide and nitrite, respectively, which interact with oxyhemoglobin to produce methemoglobin and nitrate. Thus, the end products of nitric oxide that enter the systemic circulation are predominantly methemoglobin and nitrate.

#### *Metabolism*

Methemoglobin disposition has been investigated as a function of time and nitric oxide exposure concentration in neonates with respiratory failure. The methemoglobin (MetHb) concentration-

time profiles during the first 12 hours of exposure to 0, 5, 20, and 80 ppm INOmax are shown in Figure 1.

**Figure 1: Methemoglobin Concentration-Time Profiles Neonates Inhaling 0, 5, 20 or 80 ppm INOmax**



Methemoglobin concentrations increased during the first 8 hours of nitric oxide exposure. The mean methemoglobin level remained below 1% in the placebo group and in the 5 ppm and 20 ppm INOmax groups, but reached approximately 5% in the 80 ppm INOmax group. Methemoglobin levels >7% were attained only in patients receiving 80 ppm, where they comprised 35% of the group. The average time to reach peak methemoglobin was  $10 \pm 9$  (SD) hours (median, 8 hours) in these 13 patients, but one patient did not exceed 7% until 40 hours.

#### *Elimination*

Nitrate has been identified as the predominant nitric oxide metabolite excreted in the urine, accounting for >70% of the nitric oxide dose inhaled. Nitrate is cleared from the plasma by the kidney at rates approaching the rate of glomerular filtration.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

No evidence of a carcinogenic effect was apparent, at inhalation exposures up to the recommended dose (20 ppm), in rats for 20 hr/day for up to two years. Higher exposures have not been investigated.

Nitric oxide has demonstrated genotoxicity in Salmonella (Ames Test), human lymphocytes, and after *in vivo* exposure in rats. There are no animal or human studies to evaluate nitric oxide for effects on fertility.

## 14 CLINICAL STUDIES

### 14.1 Treatment of Hypoxic Respiratory Failure (HRF)

The efficacy of INOmax has been investigated in term and near-term newborns with hypoxic respiratory failure resulting from a variety of etiologies. Inhalation of INOmax reduces the oxygenation index (OI= mean airway pressure in cm H<sub>2</sub>O × fraction of inspired oxygen concentration [FiO<sub>2</sub>]× 100 divided by systemic arterial concentration in mm Hg [PaO<sub>2</sub>]) and increases PaO<sub>2</sub> [see *Clinical Pharmacology (12.1)*].

#### NINOS Study

The Neonatal Inhaled Nitric Oxide Study (NINOS) was a double-blind, randomized, placebo-controlled, multicenter trial in 235 neonates with hypoxic respiratory failure. The objective of the study was to determine whether inhaled nitric oxide would reduce the occurrence of death and/or initiation of extracorporeal membrane oxygenation (ECMO) in a prospectively defined cohort of term or near-term neonates with hypoxic respiratory failure unresponsive to conventional therapy. Hypoxic respiratory failure was caused by meconium aspiration syndrome (MAS; 49%), pneumonia/sepsis (21%), idiopathic primary pulmonary hypertension of the newborn (PPHN; 17%), or respiratory distress syndrome (RDS; 11%). Infants ≤14 days of age (mean, 1.7 days) with a mean PaO<sub>2</sub> of 46 mm Hg and a mean oxygenation index (OI) of 43 cm H<sub>2</sub>O / mm Hg were initially randomized to receive 100% O<sub>2</sub> with (n=114) or without (n=121) 20 ppm nitric oxide for up to 14 days. Response to study drug was defined as a change from baseline in PaO<sub>2</sub> 30 minutes after starting treatment (full response = >20 mm Hg, partial = 10–20 mm Hg, no response = <10 mm Hg). Neonates with a less than full response were evaluated for a response to 80 ppm nitric oxide or control gas. The primary results from the NINOS study are presented in Table 1.

**Table 1: Summary of Clinical Results from NINOS Study**

|                             | <b>Control<br/>(n=121)</b> | <b>NO<br/>(n=114)</b> | <b>P value</b> |
|-----------------------------|----------------------------|-----------------------|----------------|
| Death or ECMO <sup>*†</sup> | 77 (64%)                   | 52 (46%)              | 0.006          |
| Death                       | 20 (17%)                   | 16 (14%)              | 0.60           |
| ECMO                        | 66 (55%)                   | 44 (39%)              | 0.014          |

\* Extracorporeal membrane oxygenation

† Death or need for ECMO was the study's primary end point

Although the incidence of death by 120 days of age was similar in both groups (NO, 14%; control, 17%), significantly fewer infants in the nitric oxide group required ECMO compared with controls (39% vs. 55%, p = 0.014). The combined incidence of death and/or initiation of ECMO showed a significant advantage for the nitric oxide treated group (46% vs. 64%, p = 0.006). The nitric oxide group also had significantly greater increases in PaO<sub>2</sub> and greater decreases in the OI and the alveolar-arterial oxygen gradient than the control group (p<0.001 for all parameters). Significantly more patients had at least a partial response to the initial administration of study drug in the nitric oxide group (66%) than the control group (26%, p<0.001). Of the 125 infants who did not respond to 20 ppm nitric oxide or control, similar percentages of NO-treated (18%) and control (20%) patients had at least a partial response to 80

ppm nitric oxide for inhalation or control drug, suggesting a lack of additional benefit for the higher dose of nitric oxide. No infant had study drug discontinued for toxicity. Inhaled nitric oxide had no detectable effect on mortality. The adverse events collected in the NINOS trial occurred at similar incidence rates in both treatment groups [see [Adverse Reactions \(6.1\)](#)]. Follow-up exams were performed at 18–24 months for the infants enrolled in this trial. In the infants with available follow-up, the two treatment groups were similar with respect to their mental, motor, audiologic, or neurologic evaluations.

### CINRGI Study

This study was a double-blind, randomized, placebo-controlled, multicenter trial of 186 term and near-term neonates with pulmonary hypertension and hypoxic respiratory failure. The primary objective of the study was to determine whether INOmax would reduce the receipt of ECMO in these patients. Hypoxic respiratory failure was caused by MAS (35%), idiopathic PPHN (30%), pneumonia/sepsis (24%), or RDS (8%). Patients with a mean PaO<sub>2</sub> of 54 mm Hg and a mean OI of 44 cm H<sub>2</sub>O / mm Hg were randomly assigned to receive either 20 ppm INOmax (n=97) or nitrogen gas (placebo; n=89) in addition to their ventilatory support. Patients who exhibited a PaO<sub>2</sub> >60 mm Hg and a pH < 7.55 were weaned to 5 ppm INOmax or placebo. The primary results from the CINRGI study are presented in Table 2.

**Table 2: Summary of Clinical Results from CINRGI Study**

|                     | <b>Placebo</b> | <b>INOmax</b> | <b>P value</b> |
|---------------------|----------------|---------------|----------------|
| ECMO <sup>*,†</sup> | 51/89 (57%)    | 30/97 (31%)   | <0.001         |
| Death               | 5/89 (6%)      | 3/97 (3%)     | 0.48           |

\* Extracorporeal membrane oxygenation

† ECMO was the primary end point of this study

Significantly fewer neonates in the INOmax group required ECMO compared to the control group (31% vs. 57%, p<0.001). While the number of deaths were similar in both groups (INOmax, 3%; placebo, 6%), the combined incidence of death and/or receipt of ECMO was decreased in the INOmax group (33% vs. 58%, p<0.001).

In addition, the INOmax group had significantly improved oxygenation as measured by PaO<sub>2</sub>, OI, and alveolar-arterial gradient (p<0.001 for all parameters). Of the 97 patients treated with INOmax, 2 (2%) were withdrawn from study drug due to methemoglobin levels >4%. The frequency and number of adverse events reported were similar in the two study groups [see [Adverse Reactions \(6.1\)](#)].

In clinical trials, reduction in the need for ECMO has not been demonstrated with the use of inhaled nitric oxide in neonates with congenital diaphragmatic hernia (CDH).

### **14.2 Ineffective in Adult Respiratory Distress Syndrome (ARDS)**

In a randomized, double-blind, parallel, multicenter study, 385 patients with adult respiratory distress syndrome (ARDS) associated with pneumonia (46%), surgery (33%), multiple trauma (26%), aspiration (23%), pulmonary contusion (18%), and other causes, with PaO<sub>2</sub>/FiO<sub>2</sub> <250 mm Hg despite optimal oxygenation and ventilation, received placebo (n=193) or INOmax (n=192), 5 ppm, for 4 hours to 28 days or until weaned because of improvements in oxygenation.

Despite acute improvements in oxygenation, there was no effect of INOmax on the primary endpoint of days alive and off ventilator support. These results were consistent with outcome data from a smaller dose ranging study of nitric oxide (1.25 to 80 ppm). INOmax is not indicated for use in ARDS.

### 14.3 Ineffective in Prevention of Bronchopulmonary Dysplasia (BPD)

The safety and efficacy of INOmax for the prevention of chronic lung disease [bronchopulmonary dysplasia, (BPD)] in neonates  $\leq$  34 weeks gestational age requiring respiratory support has been studied in four large, multi-center, double-blind, placebo-controlled clinical trials in a total of 2,600 preterm infants. Of these, 1,290 received placebo, and 1,310 received inhaled nitric oxide at doses ranging from 5-20 ppm, for treatment periods of 7-24 days duration. The primary endpoint for these studies was alive and without BPD at 36 weeks postmenstrual age (PMA). The need for supplemental oxygen at 36 weeks PMA served as a surrogate endpoint for the presence of BPD. Overall, efficacy for the prevention of bronchopulmonary dysplasia in preterm infants was not established. There were no meaningful differences between treatment groups with regard to overall deaths, methemoglobin levels, or adverse events commonly observed in premature infants, including intraventricular hemorrhage, patent ductus arteriosus, pulmonary hemorrhage, and retinopathy of prematurity.

The use of INOmax for prevention of BPD in preterm neonates  $\leq$  34 weeks gestational age is not recommended.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

INOmax (nitric oxide) is available in the following sizes:

|         |  |
|---------|--|
| Size D  | Portable aluminum cylinders containing 353 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen (delivered volume 344 liters) (NDC 64693-002-01) |
| Size 88 | Aluminum cylinders containing 1963 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen (delivered volume 1918 liters) (NDC 64693-002-02)        |

Store at 25°C (77°F) with excursions permitted between 15–30°C (59–86°F) [see USP Controlled Room Temperature].

All regulations concerning handling of pressure vessels must be followed.

Protect the cylinders from shocks, falls, oxidizing and flammable materials, moisture, and sources of heat or ignition.

### Occupational Exposure

The exposure limit set by the Occupational Safety and Health Administration (OSHA) for nitric oxide is 25 ppm, and for NO<sub>2</sub> the limit is 5 ppm.

Distributed by  
INO Therapeutics LLC  
675 McDonnell Blvd.

Hazelwood, MO 63042  
USA

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 20845/S17**

**MEDICAL REVIEW(S)**

**DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS**  
**MEDICAL OFFICER CONSULTATION**

Date: July 20, 2015  
To: Edward Fromm, CPMS  
CDER, Division of Cardiovascular and Renal Products  
From: Anthony G. Durmowicz, MD  
Clinical Team Leader, DPARP/CDER  
Through: Lydia Gilbert-McClain, MD  
Deputy Director, DPARP/CDER  
Subject: Consult for INOmax labeling change

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**General Information**

NDA/IND#: NDA 20845/S-017  
Sponsor: INO Therapeutics  
Drug Product: INOmax (inhaled nitric oxide)  
Request From: Division of Cardiovascular and Renal products  
Date of Request: May 18, 2015  
Materials: BPD-301 Study Report, Proposed labeling changes, NIH consensus  
Reviewed: paper on the use of iNO in premature infants, mortality data from  
similar BPD-prevention trials, DCRP clinical and statistical reviews  
of BPD-301 study report.

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**Introduction**

This is a Medical Officer Consultation intended to respond to a request for consultation issued by the Division of Cardiovascular and Renal Products (DCRP) regarding updating the INOmax (inhaled nitric oxide, iNO) label to reflect safety data from a completed phase 3 clinical trial (BPD-301) that investigated the use of inhaled nitric oxide (iNO) in premature infants for the prevention of chronic lung disease related to prematurity (bronchopulmonary dysplasia or BPD).

**Background**

INOmax is nitric oxide gas for inhalation marketed at concentrations of 100 and 800 parts per million in nitrogen. It is a potent vasodilator which, when inhaled, acts locally on the pulmonary circulation to decrease pulmonary artery pressure and vascular resistance. It was initially approved by the FDA (DCRP) in 1999 for the treatment of term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension”.

In addition to its use in the treatment of term and near-term neonates with evidence of pulmonary hypertension, the NDA holder, INO Therapeutics, and other academic

investigators have extensively studied the use of iNOMax for the prevention of chronic lung disease (Bronchopulmonary Dysplasia, BPD) in preterm infants gestational ages of 24 to 34 weeks. The functional hypothesis, based on in vitro and experimental animal data that nitric oxide may have anti-inflammatory properties and promote lung growth, is that inhaled nitric oxide in the preterm neonate will act by decreasing lung inflammation and improve pulmonary angiogenesis and alveolarization and, thus, prevent the development of chronic lung disease associated with premature birth.

To date there have been a fairly large number of clinical studies looking at the effect of iNO on the development of chronic lung disease related to prematurity with mostly neutral or negative results. In October 2010, an NIH Consensus Conference was held in Bethesda, MD that discussed the evidence for iNO therapy for premature infants and concluded that the evidence for benefit (reduced severity or prevention of BPD) was not sufficient to recommend its use. One NIH-sponsored study (PI Roberta Ballard MD), which was conducted a bit differently than most others, infants were not enrolled until at least 5 days old after it could be determined that they would be at risk for BPD, were treated with relatively high (20 PPM) doses of iNO over 24 days suggested a benefit. INO Therapeutics subsequently conducted Study BPD-301, modeled after the Ballard study, (b) (4) Following is a very brief description of the study (for more detail please see the DCRP statistical and clinical reviews by Ququan Liu and Maryann Gordon, respectively) followed by a list of the proposed labeling changes and DPARP discussion regarding inclusion in the INOMax label.

### **Study BPD-301**

The primary objective of this trial was to examine the efficacy of iNO in preterm infants < 30 weeks gestational age (GA) with a birth weight of < 1,250 grams who required mechanical ventilation or positive pressure support on Days 5 to 14 after birth. The study was modeled after the NIH-sponsored study published by Roberta Ballard in 2006, which is the only previous large randomized trial that demonstrated a potential for iNO to reduce the incidence of BPD. In this light, instead of being enrolled immediately after birth as in other studies, infants who met entry criteria were enrolled any point during days 5 to 14 after birth and randomized to receive iNO starting at a relatively high iNO dose of 20 parts per million (ppm), or matching control. All infants received 24 days of therapy following a dose reduction schedule.

The primary efficacy endpoint was defined as “alive without BPD at 36 weeks GA.” Results demonstrated no significant treatment effect with 70/222 (31.5%) successes in the placebo group and 80/229 (34.9%) successes in the iNO group.

A total of 45 deaths occurred in the trial; 19/222 (8.6%) subjects in the placebo group and 26/229 (11.4%) subjects in the iNO group. The majority of these deaths occurred by Week 36 GA; 15 (6.8%) deaths in the placebo group and 19 (8.3%) deaths in the iNO group (the incidence of deaths in subjects at Week 36 GA was used in the determination of the primary efficacy endpoint). There was a significant between-treatment difference with regard to race for subjects who died by 36 weeks GA ( $p = 0.036$ ) with a numerical

imbalance in deaths favoring placebo in the subgroup of white subjects at 36 weeks GA (placebo: 2/15, 13.3%; iNO: 11/19, 57.9%). This imbalance was driven by the subgroup of very premature (< 27 weeks GA) white male infants.

Based on the results of this study, INO Therapeutics submitted a NDA supplement which included several proposed label changes. The following labeling revisions relevant to DPARP are proposed:



- Clinical Studies (Section 14)
  - Updating the Prevention of BPD subsection to include the BPD-301 study noting that there were no meaningful differences in overall mortality between infants treated with iNO and control

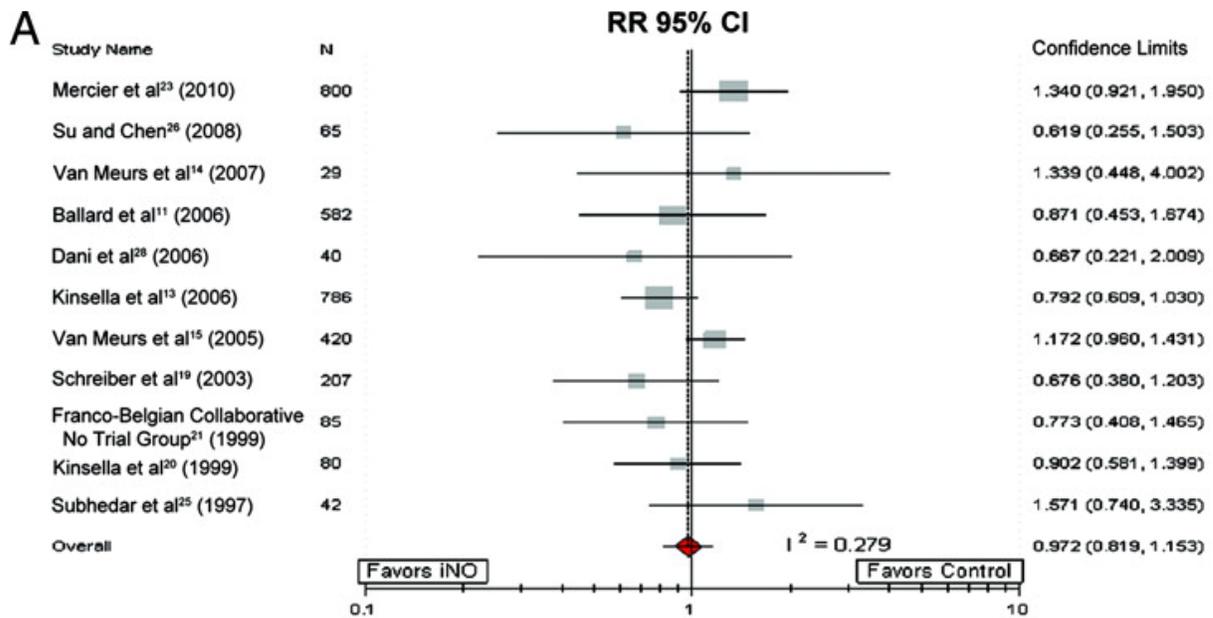


## **Discussion**

### *Death in studies of iNO in premature infants*

At the October 2010, NIH Consensus Conference for use of iNO in premature infants, a meta-analysis was presented that evaluated risk of death and BPD at 36 weeks gestational age in 10 previously conducted clinical studies in over 2300 infants. The analysis found that no significant increase or decrease in survival rates (relative risk 0.932 (95% CI 0.788, 1.101)). The report was subsequently updated with the addition of another study and published in the journal Pediatrics. The figure below, adapted from Figure 2 of that publication, shows that overall there is no difference in death between infants treated with iNO compared to placebo.

**Figure 1. Meta-Analysis of Death in Clinical Studies of iNO in Premature Infants\***



\*adapted from Donohue PK, et al, Inhaled nitric oxide in preterm infants: A systematic review. Pediatrics 2011; 127:e414-e422.

From the Figure above one can see while the point estimates for death appear to favor infants treated with iNO, overall there is little to no impact of iNO on death for infants enrolled in the studies noted above. As for study BPD-301, nominally more deaths occurred in patients treated with iNOmax than placebo (Table 1).

**Table 1. Deaths in Study BPD-301**

| Death*         | Placebo<br>N=222 | iNOmax<br>N=229 |
|----------------|------------------|-----------------|
| On treatment   | 4 (1.8%)         | 13/229 (5.7%)   |
| At 36 Weeks GA | 15 (6.8%)        | 19 (8.3%)       |
| At 24 months   | 19 (8.6%)        | 26 (11.4%)      |

\*on treatment defined as during the 24-day treatment period when infants would be between 5 and 38 days of age; 36 weeks GA was the time point at which efficacy was determined when infants, an infant born at 28 weeks would be 8 weeks old; the 24 month time point was at the time of long-term follow-up.

For the overall population, these differences were not statistically significant ( $p=0.337$  at 24 month time point) but the Applicant notes that in post hoc analyses there was a racial imbalance with iNO-treated White infants having a higher mortality rate (15/120, 12.5%) compared to those who received placebo (2/84, 2.4%) that was statistically significant ( $p= 0.0098$ ). Note that the study was not stratified by race and there was a statistically significant imbalance in Race between treatment groups with 52.4% of White infants in the iNO group and 38.3% in the placebo group. The difference appears to be driven by an imbalance among White males < 27 weeks GA with mortality rates of 26.1% (12/46) and 2.7% (1/37) for the iNO and placebo groups, respectively (Module 2.7.4, Clinical Summary of Safety, p. 49 of 323). It is also notable that in additional analyses, the Applicant notes that there were no differences in mortality in White infants < 27 weeks

GA who were enrolled in 3 other studies (total 2598 infants), the Applicant has data for (Module 2.7.4, Clinical Summary of Safety, p. 126 of 323).

### **Summary/Conclusions**

Putting all the accumulated evidence in context, it appears that across at least 11 clinical studies there is no evidence that treatment of premature infants with iNO results in increased mortality with an overall relative risk of 0.972 nominally favoring the iNO treated group (Figure 1). Additionally, individual and combined data from the studies the Applicant has access to (Ballard NIH-sponsored study and 2 Applicant sponsored studies INOT-25 and INOT-27) do not show an imbalance (per Applicant analyses) in deaths in very premature White males as was observed in Study BPD-301. It is difficult to determine why one would see such an imbalance in Study BPD-301 although there were a larger number of White infants treated with iNO (52.4%) compared to placebo (38.3%). The question then becomes what to do with the additional data from this newly submitted Study BPD-301, where, in the face of no difference in overall mortality in BPD-301 or meta-analyses of other studies conducted in premature infants, post hoc analyses of Study BPD-301 show a mortality risk for White male infants born at < 27 weeks GA?

There are 2 main labeling changes relevant to DPARP; the addition of a Warning and Precaution in Section 5 which generalizes the post hoc analysis from Study BPD-301 by noting that there is an increased mortality risk in white male infants <27 weeks GA at birth and inclusion of the post hoc analysis from Study BPD-301 in Section 14 of the label. It is DPARP's opinion that these findings from post hoc analyses of a single study, when taken in context of the overall clinical experience do not warrant a new Warning and Precaution in the INOmax label. With regard to the addition of the description of the results of the post hoc analysis in Section 14, DPARP does not have any strong objections given the Applicant simply states the results and mentions that overall mortality was no different. However, since just inclusion of such data by itself tend to implicate a mortality problem in White male infants that likely does not exist based on the data from other studies, one could consider not including the post hoc analysis and simply state there was no imbalance in mortality for the now four studies mentioned in the label.

Please feel free to contact DPARP with any questions.

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/s/  
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ANTHONY G DURMOWICZ  
07/21/2015

LYDIA I GILBERT MCCLAIN  
07/21/2015

NDA# 20845  
Review of protocol: IK-3001-BPD-301  
Medical reviewer: Maryann Gordon, MD

### **Summary**

No significant treatment effect was observed for the primary outcome variable.

A total of 45 deaths occurred in the trial (clinical database); 19/222 (8.6%) subjects in the placebo group and 26/229 (11.4%) subjects in the iNO group. The majority of these deaths occurred by Week 36 GA; 15 (78.9%) of the 19 deaths in the placebo group and 19 (73.1%) of the 26 deaths in the iNO group. The incidence of deaths in subjects at Week 36 GA was used in the determination of the primary efficacy endpoint. There was a statistically significant between-treatment difference with regard to race for subjects who died by 36 weeks GA ( $p = 0.036$ ) with a numerical imbalance in deaths favoring placebo in the subgroup of white subjects at 36 weeks GA (placebo: 2/15, 13.3%; iNO: 11/19, 57.9%).

### **Background**

Primary objective:

The primary objective of this trial was to examine the efficacy of inhaled nitric oxide (iNO) in preterm infants < 30 weeks gestational age (GA) with a birth weight of < 1,250 grams who required mechanical ventilation or positive pressure support on Days 5 to 14 after birth.

Multicenter, double-blind, placebo-controlled, randomized clinical trial. Infants who met all enrollment criteria at any point during Days 5 to 14 after birth were randomized to iNO starting at 20 parts per million (ppm), or matching placebo, by means of a blinded INOvent® delivery device. All infants received 24 days of therapy following a dose reduction schedule.

Study drug was weaned from 20 ppm to 10 ppm between 72 to 96 hours of treatment. The next wean was to 5 ppm on Day 10. If the infant deteriorated after any dose reduction, he/she was put back on the previous treatment and weaning was reattempted as tolerated. The total duration of treatment was 24 days.

Primary Efficacy Variable:

- Survival without BPD at 36 weeks GA using a physiologic assessment

The primary efficacy outcome was treatment success defined as “alive without BPD at 36 weeks GA.” No significant treatment effect was observed for the primary outcome variable, with 70/222 (31.5%) successes in the placebo group and 80/229 (34.9%) successes in the iNO group. Sensitivity analysis and subgroup analysis based on demographic and baseline characteristics (age group, type of ventilation at Baseline, and sex) showed no significant treatment effect on the primary efficacy response in this trial.

A total of 45 deaths occurred in the trial (clinical database); 19/222 (8.6%) subjects in the placebo group and 26/229 (11.4%) subjects in the iNO group. The majority of these deaths occurred by Week 36 GA; 15 (78.9%) of the 19 deaths in the placebo group and 19 (73.1%) of the 26 deaths in the iNO group. The incidence of deaths in subjects at Week 36 GA was used in the determination of the primary efficacy endpoint. There was a statistically significant between-treatment difference with regard to race for subjects who died by 36 weeks GA ( $p = 0.036$ ) with a numerical imbalance in deaths favoring placebo in the subgroup of white subjects at 36 weeks GA (placebo: 2/15, 13.3%; iNO: 11/19, 57.9%).

Inhaled NO, started at 20 ppm within 5 to 14 days after birth and maintained for 24 days in high-risk, preterm infants requiring airway pressure support, did not increase the rate of survival without BPD, nor did it improve other secondary efficacy outcome measures compared with placebo. In this trial, iNO was tolerated with a safety profile similar to that of placebo despite the numerical imbalance in mortality during the 24-day treatment period and in a single subgroup of very premature (< 27 weeks GA) white male infants, as the safety profile revealed no other unexpected safety findings.

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/s/  
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MARYANN GORDON  
03/13/2015

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 20845/S17**

**STATISTICAL REVIEW(S)**



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

**NDA/Serial Number:** 020845 / S\_017

**Drug Name:** INOmax® (nitric oxide) for inhalation

**Indication(s):** Bronchopulmonary Dysplasia (BPD) in Preterm Infants Requiring Mechanical Ventilation or Positive Pressure Support on Days 5 to 14 After Birth

**Applicant:** INO Therapeutics LLC

**Date(s):** Date of Document: December 11, 2014  
PDUFA Due Date: October 11, 2015

**Review Priority:** Standard

**Biometrics Division:** Biometrics I, HFD-710

**Statistical Reviewer:** Ququan Liu, M.D., M.S.

**Concurring Reviewers:** James Hung, Ph.D.

**Medical Division:** Division of Cardio-Renal Drug Products, HFD-110

**Clinical Team:** Maryann Gordon, M.D, Norman Stockbridge, M.D., Ph.D.

**Project Manager:** Edward Fromm, R.Ph., RAC

**Keywords:** INHALED NITRIC OXIDE, BPD, Preterm Infants

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## 1. EXECUTIVE SUMMARY

### 1.1 Conclusions and Recommendations

(b) (4)

### 1.2 Brief Overview of Clinical Studies

This was labeling supplement that proposes labeling revisions based on the efficacy study results of IK 300-1-BPD-301.

The primary objective of Study IK 300-1-BPD-301 was to examine the efficacy of inhaled nitric oxide (iNO) in preterm infants < 30 weeks gestational age (GA) with birth weight < 1250 grams who required mechanical ventilation or positive pressure support on Days 5 to 14 after birth. The efficacy was evaluated by survival without BPD at 36 weeks GA.

The sponsor intended to propose revisions to the INOmax prescribing information including changes to the Highlights, Warnings and Precautions, and Clinical Studies sections.

### 1.3 Statistical Issues and Findings

No Statistical issue was identified. (b) (4)

## 2. INTRODUCTION

### 2.1 Overview

Bronchopulmonary dysplasia (BPD) is the most common cause of chronic lung disease in infants, and is almost universally a disease of preterm infants, especially infants who weigh < 1,500 grams and are < 30 weeks gestational age (GA) at birth. These infants are commonly subject to respiratory support with mechanical ventilation and supplemental oxygen (O<sub>2</sub>), leading to barotrauma, volutrauma, and increased oxidative stress, which are known to cause lung injury. Inhaled nitric oxide (iNO) is a potent and selective pulmonary vasodilator and will also improve oxygenation by improving ventilation perfusion matching in the failing lung. iNO was approved for the treatment of hypoxic respiratory failure in the term and near-term newborn, it has been suggested that iNO might also benefit the sick, preterm infant with underdeveloped lungs by reducing the incidence or severity of BPD.

(b) (4)

## 2.2 Data Sources

The sponsor's SAS datasets were stored in the directory of <\\cdsesub4\NONECTD\NDA020845\5748781> of the Center's electronic document room.

## 3. STATISTICAL EVALUATION

### 3.1 Data and Analysis Quality

Data and analysis quality is acceptable. Consistent results can be generated from both raw and derived data.

### 3.2 Evaluation of Efficacy

#### 3.2.1 Primary Study Objective

The primary objective of this trial was to examine the efficacy of iNO in preterm infants < 30 weeks GA with birth weight < 1,250 grams, who required mechanical ventilation or positive pressure support on Days 5 to 14 after birth.

#### 3.2.2 Study Design

This was a multicenter, double-blind, placebo-controlled, randomized clinical trial. All infants < 30 weeks GA at birth were screened for enrollment. Randomization was stratified by center and GA (< 27 weeks GA and 27 through 30 weeks GA). All infants were to receive 24 days therapy following a dose reduction schedule. The primary outcome measure was survival without BPD at 36 weeks GA using a physiologic assessment of BPD.

#### 3.2.3 Efficacy Measures and Analyses

1) Primary Efficacy Endpoint: The primary efficacy variable was survival without BPD at 36 weeks GA using a physiological assessment of BPD. A subject was considered to have BPD if the subject had any of the following at 36 weeks GA:

- On mechanical ventilation or CPAP
- Effective FiO<sub>2</sub> ≥ 30%
- Timed O<sub>2</sub> reduction test with any saturation < 90% in room air for 5 consecutive minutes or < 80% for 15 seconds within 30 minutes
- BPD per the Principal Investigator's clinical assessment with specific explanation

A subject who was alive without BPD at 36 weeks GA was counted as a success, and a failure if the subject died, had BPD at 36 weeks GA, or had received open-label commercial iNO during the blinded trial.

2) Secondary Efficacy Endpoints: The secondary efficacy endpoints included the following assessments:

- Days of air pressure support for lung disease during birth hospitalization
- Days of hospitalization during birth hospitalization
- Use of postnatal corticosteroids for respiratory insufficiency (including dose and duration of therapy) during birth hospitalization
- Days of O2 use during birth hospitalization
- Severity of BPD (as defined by FiO2 requirement) among survivors at 36 weeks GA as determined by the level of support needed to maintain arterial O2 saturation (SaO2)  $\geq$  90%
- Disease status at Weeks 36, 40, and 44 GA (subjects categorized as either discharged from hospital, continued hospitalization without continued respiratory support, continued hospitalization with respiratory support consisting of O2 only, continued hospitalization with any airway pressure support, or death)
- Use of respiratory medications, O2, and days of all hospitalizations at 12 months and 18 to 24 months of corrected age (chronologic age measured from 40 weeks GA)

### 3) Statistical Analysis Methodology

- Primary efficacy endpoint: The generalized estimating equation (GEE) for logistic regression was used. Measurements from the same birth (such as twins and triplets) were considered as repeat measurements and the exchangeable working correlation structure was specified in the GEE analysis. The GA strata and treatment effect were included in the model. The Cochran–Mantel–Haenszel (CMH) test stratified by GA strata was utilized to verify the primary efficacy result.
- Secondary efficacy endpoints: The GEE for logistic regression was used to analyze the binary response variables and a mixed-effects model with repeated measures was used to analyze other variables.
- Multiplicity adjustment: A hierarchical gate keeping procedure was applied to control the overall type I error rate of 0.05, in the order of :
  1. Survival without BPD at 36 weeks GA
  2. Days of airway pressure support for lung disease during birth hospitalization
  3. Days of hospitalization during birth hospitalization
  4. Use of postnatal corticosteroids for respiratory insufficiency during birth hospitalization
- Handling missing data: Subjects with missing primary efficacy assessment or who received commercial iNO therapy during the blinded treatment period were considered as failures in the statistical analysis.

#### 3.2.4 Patient Disposition, Demographic and Baseline Characteristics

##### 1) Patient Disposition

A total of 3,458 subjects were screened. Of these subjects, 451 (ITT) subjects (13.0%) were enrolled and randomized, 222 to the placebo group and 229 to the iNO group. A total of 449 (449/451=99.6%) randomized subjects received study drug; 220 (220/222=99.1%) in the placebo group and 229 (229/229=100%) in the iNO group (Table 1). 91.4% subjects in the ITT population completed the trial through 36 weeks GA, 91.9% in the placebo group and 90.8% in the iNO group (Table 2).

**Table 1 Study Population**

| Population                                   | Placebo<br>n (%) | iNO<br>n (%) | Total<br>n (%) |
|--|------------------|--------------|----------------|
| All subjects enrolled                        | 222 (100)        | 229 (100)    | 451 (100)      |
| Intent-to-treat: all randomized subjects     | 222 (100)        | 229 (100)    | 451 (100)      |
| Safety: all subjects who received study drug | 220 (99.1)       | 229 (100)    | 449 (99.6)     |

(Source: Sponsor's Table 3, confirmed by the reviewer's analysis)

**Table 2 Study Completion at 36 Weeks Gestational Age –ITT Population**

| Category                | Placebo<br>N = 222<br>n (%) | iNO<br>N = 229<br>n (%) | Total<br>N = 451<br>n (%) |
|-------------------------|-----------------------------|-------------------------|---------------------------|
| Completed               | 204 (91.9)                  | 208 (90.8)              | 412 (91.4)                |
| Did Not Complete:       | 18 (8.1)                    | 21 (9.2)                | 39 (8.6)                  |
| Consent withdrawn       | 3 (1.4)                     | 2 (0.9)                 | 5 (1.1)                   |
| Request of Investigator | 0 (0.0)                     | 0 (0.0)                 | 0 (0.0)                   |
| Death                   | 15 (6.8)                    | 19 (8.3)                | 34 (7.5)                  |
| Lost to follow-up       | 0                           | 0                       | 0                         |

(Source: Sponsor's Table 4, confirmed by the reviewer's analysis)

## 2) Patient Demographic and Baseline Characteristics

Demographic and baseline characteristics were similar between treatment groups in the ITT Population with the exception of race. There were more whites in the iNO group (52.4%) than in the placebo group (38.3%). Mean birth weight was greater in the placebo (Table 3).

**Table 3 Demographic and Baseline Characteristics (ITT)**

| Category<br>Parameter or Subcategory      | Placebo<br>N = 222 | iNO<br>N = 229 | Total<br>N = 451 | p value <sup>a</sup> |
|---|--------------------|----------------|------------------|----------------------|
| Gestational Age (weeks)                   |                    |                |                  |                      |
| N   | 222                | 229            | 451              |                      |
| Mean (SD)                                 | 25.6 (1.52)        | 25.6 (1.43)    | 25.6 (1.48)      | 0.765                |
| Median                                    | 25.6               | 25.4           | 25.6             |                      |
| Range                                     | 23.0 - 29.9        | 22.9 - 29.4    | 22.9 - 29.9      |                      |
| Gestational Age Category, n (%)           |                    |                |                  |                      |
| < 27 weeks                                | 176 (79.3)         | 187 (81.7)     | 363 (80.5)       | 0.554                |
| ≥ 27 weeks                                | 46 (20.7)          | 42 (18.3)      | 88 (19.5)        |                      |
| Sex, n (%)                                |                    |                |                  |                      |
| Male                                      | 116 (52.3)         | 115 (50.2)     | 231 (51.2)       | 0.707                |
| Female                                    | 106 (47.7)         | 114 (49.8)     | 220 (48.8)       |                      |
| Race, n (%)                               |                    |                |                  |                      |
| White                                     | 85 (38.3)          | 120 (52.4)     | 205 (45.5)       | 0.001                |
| Black                                     | 62 (27.9)          | 55 (24.0)      | 117 (25.9)       |                      |
| Hispanic                                  | 48 (21.6)          | 40 (17.5)      | 88 (19.5)        |                      |
| American Indian Or Alaska Native          | 12 (5.4)           | 1 (0.4)        | 13 (2.9)         |                      |
| Asian                                     | 5 (2.3)            | 1 (0.4)        | 6 (1.3)          |                      |
| Native Hawaiian Or Other Pacific Islander | 0                  | 1 (0.4)        | 1 (0.2)          |                      |
| Other                                     | 10 (4.5)           | 11 (4.8)       | 21 (4.7)         |                      |
| Length at Birth (centimeters)             |                    |                |                  |                      |
| N   | 218                | 223            | 441              |                      |
| Mean (SD)                                 | 32.2 (2.70)        | 32.1 (2.74)    | 32.1 (2.72)      | 0.945                |
| Median                                    | 32.0               | 32.0           | 32.0             |                      |
| Range                                     | 20.0 - 39.0        | 21.0 - 41.0    | 20.0 - 41.0      |                      |
| Weight at Birth (grams)                   |                    |                |                  |                      |
| N   | 221                | 229            | 450              |                      |
| Mean (SD)                                 | 749.7 (163.90)     | 723.6 (159.90) | 736.5 (162.22)   | 0.074                |
| Median                                    | 740.0              | 710.0          | 727.5            |                      |
| Range                                     | 380.0 - 1230.0     | 375.0 - 1215.0 | 375.0 - 1230.0   |                      |
| Birth Weight Category, n (%)              |                    |                |                  |                      |
| < 750 grams                               | 119 (53.6)         | 139 (60.7)     | 258 (57.2)       | 0.320                |
| 750 through 999 grams                     | 82 (36.9)          | 71 (31.0)      | 153 (33.9)       |                      |
| ≥ 1000 grams                              | 20 (9.0)           | 19 (8.3)       | 39 (8.6)         |                      |

**Table 3 Demographic and Baseline Characteristics (ITT) (Continued)**

| Category<br>Parameter or Subcategory      | Placebo<br>N = 222 | iNO<br>N = 229 | Total<br>N = 451 | p value <sup>a</sup> |
|---|--------------------|----------------|------------------|----------------------|
| Head Circumference at Birth (centimeters) |                    |                |                  |                      |
| N   | 219                | 223            | 442              |                      |
| Mean (SD)                                 | 22.9 (1.89)        | 22.7 (1.67)    | 22.8 (1.78)      | 0.445                |
| Median                                    | 22.5               | 22.5           | 22.5             |                      |
| Range                                     | 19.0 - 31.0        | 19.0 - 28.5    | 19.0 - 31.0      |                      |
| Apgar Score at 1 Minute                   |                    |                |                  |                      |
| N   | 220                | 223            | 443              |                      |
| Mean (SD)                                 | 3.7 (2.19)         | 4.0 (2.25)     | 3.9 (2.23)       | 0.117                |
| Median                                    | 4.0                | 4.0            | 4.0              |                      |
| Range                                     | 0.0 - 9.0          | 0.0 - 9.0      | 0.0 - 9.0        |                      |
| Apgar Score at 5 Minutes                  |                    |                |                  |                      |
| N   | 220                | 223            | 443              |                      |
| Mean (SD)                                 | 6.2 (1.96)         | 6.4 (1.83)     | 6.3 (1.89)       | 0.444                |
| Median                                    | 7.0                | 7.0            | 7.0              |                      |
| Range                                     | 1.0 - 9.0          | 1.0 - 10.0     | 1.0 - 10.0       |                      |

(Source: Sponsor's Table 6, confirmed by the reviewer's analysis)

### 3.2.5 Sponsor's Primary Efficacy Results

There was no statistically significant difference between treatment groups in reduction of BPD defined as alive without BPD at 36 weeks GA (p=0.427) (Tables 4 & 5).

**Table 4 Primary Endpoint: Alive without BPD at 36 Weeks GA**

| Outcome   | Placebo<br>N = 222<br>n (%) | iNO<br>N = 229<br>n (%) |
|---|-----------------------------|-------------------------|
| Success: Alive without BPD at 36 weeks GA             | 70 (31.5)                   | 80 (34.9)               |
| Failure: Death or had BPD at 36 weeks GA <sup>b</sup> | 152 (68.5)                  | 149 (65.1)              |

(Source: Sponsor's Table 9, confirmed by the reviewer's analysis)

**Table 5 Primary Outcome Evaluated by Generalized Estimating Equation (ITT)**

| Model Variable             | Coefficient | Standard Error | p value <sup>a</sup> |
|----------------------------|-------------|----------------|----------------------|
| Intercept                  | -0.6        | 0.23           | 0.010                |
| GA Strata                  | -0.2        | 0.24           | 0.316                |
| Treatment (iNO vs Placebo) | 0.2         | 0.20           | 0.427                |

Note: Subjects with missing primary outcome or who crossed over to open-label iNO during the blinded treatment period were considered as failures.

<sup>a</sup> Based on the generalized estimating equation for logistic regression of the primary outcome with measurements from multiple births as the repeat measurements. The GA strata and treatment effect are included in the model.

GA = gestational age; iNO = inhaled nitric oxide.

(Source: Sponsor’s Table 10, confirmed by the reviewer’s analysis)

3.2.6 Reviewer’s Results

This reviewer verified the sponsor’s results (see Table 6) and concurred with their conclusion.

**Table 6 Analysis of Primary Efficacy Endpoint (ITT)**

| Model Variable         | Coefficient (SE) | P-value |
|------------------------|------------------|---------|
| <b>Intercept</b>       | 0.59 (0.24)      | 0.013   |
| <b>GA strata</b>       | 0.24 (0.25)      | 0.333   |
| <b>iNO vs. Placebo</b> | -0.16 (0.20)     | 0.427   |

(Source: The reviewer’s analysis)

3.2.7 Conclusion

This is a negative study. [Redacted] (b) (4)

3.3 Evaluation of Safety

Please refer to Dr. Gordon’s review for safety assessment.

4. SUMMARY AND CONCLUSIONS

4.1 Statistical Issues and Collective Evidence

No statistical issue was identified. [Redacted] (b) (4)

## 4.2 Conclusions and Recommendations

(b) (4)



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/s/  
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QUQUAN LIU  
06/22/2015

HSIEN MING J HUNG  
06/23/2015

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 20845/S17**

**OTHER REVIEW(S)**

RHPM NDA Supplement Overview

INOmax (nitric oxide) for inhalation

**NDA 20845/S-016 & 017**

**Applicant:** Mallinckrodt Hospital Products IP Limited  
U.S. Agent: INO Therapeutics

**Classification:** S-017 (SE8-labeling supplement with clinical data)

**Review Classification:** S-017 - Standard (10 month review)

**Date of Applications:** December 5, 2014 (S-016)  
December 9, 2014 (S-017)

**Receipt Dates:** December 8, 2014 (S-016)  
December 11, 2014 (S-017)

**User Fee Goal Date:** October 11, 2015 (S-017)

**BACKGROUND**

**S-016**

This labeling supplement proposed the following:

The removal of the 100 ppm nitric oxide concentration from the labeling and revisions to the **DOSAGE AND ADMINISTRATION** and **WARNINGS AND PRECAUTIONS** sections of the INOmax package insert.

Dr. Gordon reviewed the supplement and had the following recommendations and comments:

The Agency does not typically include information in the label about checking expiration dates. The need for periodic non-FDA mandated training programs is already included in the label. The changes to the first sentence under this section are acceptable. Regarding the validated ventilator systems, the following statement could be added:

Only validated ventilator systems should be used in conjunction with INOmax. Consult the Nitric Oxide Delivery System label or call xxx.xxx.xxx/visit inomax.com for a current list of validated systems.

The remaining changes for the rest of section 2 are not necessary.  
The changes for section 5.3 are not needed.  
The removal of the 100 ppm strength is acceptable.

The Division issued a complete response letter on June 4, 2015 with marked-up labeling showing the Division's labeling revisions per Dr. Gordon's review.

**S-017**

This efficacy supplement proposed revisions to the labeling based on the clinical study entitled "*Bronchopulmonary Dysplasia (BPD) in Preterm Infants Requiring Mechanical Ventilation or Positive Pressure Support on Days 5 to 14 After birth (IK-3001-BPD-301)*". These revisions to the labeling were:

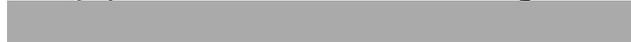


- Clinical Studies (Section 14)
  - Updating the Prevention of BPD subsection to include the BPD-301 study noting that there were no meaningful differences in overall mortality between infants treated with iNO and control.



Dr. Gordon reviewed the supplement. She noted that the primary efficacy outcome was treatment success defined as "alive without BPD at 36 weeks GA." Dr. Gordon found no significant treatment effect was observed for the primary outcome variable, with 70/222 (31.5%) successes in the placebo group and 80/229 (34.9%) successes in the iNO group. Sensitivity analysis and subgroup analysis based on demographic and baseline characteristics (age group, type of ventilation at Baseline, and sex) showed no significant treatment effect on the primary efficacy response in this trial. She indicated that there should be not revisions to the labeling based on this safety study.

A consult review completed by the Division of Pulmonary and Allergy Products (Dr. Anthony Durmowicz- July 21, 2015) also agreed that labeling changes to the labeling from the study were not warranted.

Dr. Ququan Liu noted that this was a negative study.  

### **User Fee**

The applicant received an Orphan waiver for the user fee for S-017.

### **Action/Conclusion**

The only labeling item of contention for both S-016 and S-017 between the applicant and the Division was the statement in section 5.3 Airway Injury from Nitrogen Dioxide <sup>(b) (4)</sup>



Agreement was reached between the Division and the applicant with the following revisions so the section 5.3 of the PI now reads as follows:

Nitrogen dioxide (NO<sub>2</sub>) forms in gas mixtures containing NO and O<sub>2</sub>.

Nitrogen dioxide may cause airway inflammation and damage to lung tissues. If there is an unexpected change in NO<sub>2</sub> concentration, or if the NO<sub>2</sub> concentration reaches 3 ppm when measured in the breathing circuit, then the delivery system should be assessed in accordance with the Nitric Oxide Delivery System O&M Manual troubleshooting section, and the NO<sub>2</sub> analyzer should be recalibrated. The dose of INOmax and/or FiO<sub>2</sub> should be adjusted as appropriate.

An approval letter for both supplements was signed by Dr. Stockbridge on October 9, 2015.

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Edward J. Fromm, R.Ph., RAC  
Regulatory Health Project Manager

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/s/  
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EDWARD J FROMM  
11/05/2015

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 20845/S17**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 20845

SUPPL # 017

HFD # 110

Trade Name INOmax

Generic Name Nitric Oxide for inhalation

Applicant Name Mallinckrodt Hospital Products

Approval Date, If Known: October 9, 2015

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES X

NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES

NO X

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

Safety-related labeling changes from study "*Bronchopulmonary Dysplasia (BPD) in Preterm Infants Requiring Mechanical Ventilation or Positive Pressure Support on Days 5 to 14 After Birth (IK-3001-BPD-301)*"

d) Did the applicant request exclusivity?

YES  NO X

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

Yes

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO X

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

N/A

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

*Bronchopulmonary Dysplasia (BPD) in Preterm Infants Requiring Mechanical Ventilation or Positive Pressure Support on Days 5 to 14 After Birth (IK-3001-BPD-301)*

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

*Bronchopulmonary Dysplasia (BPD) in Preterm Infants Requiring Mechanical Ventilation or Positive Pressure Support on Days 5 to 14 After Birth (IK-3001-BPD-301)*

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1  
IND # 63096      YES       ! NO   
! Explain:

Investigation #2  
IND #      YES       ! NO   
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1  
!  
!  
YES  ! NO   
Explain: ! Explain:

Investigation #2  
!  
!  
YES  ! NO   
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

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Name of person completing form: Edward Fromm, R.Ph., RAC  
Title: Chief, Project Management Staff, Division of Cardiovascular and Renal Products  
Date: 02/22/16 (revised)

Name of Division Director signing form: Norman Stockbridge, M.D., Ph.D  
Title: Director, Division of Cardiovascular and Renal Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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/s/  
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EDWARD J FROMM  
02/22/2016

NORMAN L STOCKBRIDGE  
02/22/2016

February 23, 2016

This REV-SUMMARY-03 (Exclusivity Summary) for NDA 20845 Supplement-17 was replaced by the corrected review dated 2/22/2016.

The new version of the summary includes revisions to Pediatric Exclusivity section to reflect the previously granted pediatric exclusivity.

## EXCLUSIVITY SUMMARY

NDA # 20845

SUPPL # 017

HFD # 110

Trade Name INOmax

Generic Name Nitric Oxide for inhalation

Applicant Name Mallinckrodt Hospital Products

Approval Date, If Known: October 9, 2015

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES X

NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES

NO X

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

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Safety-related labeling changes from study "*Bronchopulmonary Dysplasia (BPD) in Preterm Infants Requiring Mechanical Ventilation or Positive Pressure Support on Days 5 to 14 After Birth (IK-3001-BPD-301)*"

d) Did the applicant request exclusivity?

YES  NO X

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO X

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO X

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

N/A

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

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YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not

essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

*Bronchopulmonary Dysplasia (BPD) in Preterm Infants Requiring Mechanical Ventilation or Positive Pressure Support on Days 5 to 14 After Birth (IK-3001-BPD-301)*

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:



Investigation #2

YES

Explain:

!

!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

---

Name of person completing form: Edward Fromm, R.Ph., RAC  
Title: Chief, Project Management Staff, Division of Cardiovascular and Renal Products  
Date: 10/19/15

Name of Division Director signing form: Norman Stockbridge, M.D., Ph.D  
Title: Director, Division of Cardiovascular and Renal Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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/s/  
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EDWARD J FROMM  
10/19/2015

NORMAN L STOCKBRIDGE  
10/19/2015

## REQUEST FOR CONSULTATION

TO (Office/Division): **Division of Pulmonary, Allergy, and Rheumatology Products**

FROM (Name, Office/Division, and Phone Number of Requestor): **Edward Fromm, Division of Cardiovascular and Renal Products, (301) 796-1072**

DATE  
May 18, 2015

IND NO.

NDA NO.  
20845/S-017

TYPE OF DOCUMENT  
Study Report/Labeling

DATE OF DOCUMENT  
December 11, 2014

NAME OF DRUG  
**INOmax (nitric oxide) for inhalation**

PRIORITY CONSIDERATION  
Standard

CLASSIFICATION OF DRUG  
SE-8

DESIRED COMPLETION DATE  
July 18, 2015

NAME OF FIRM: **INO Therapeutics**

### REASON FOR REQUEST

#### I. GENERAL

- |  |   |  |
|--|---|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING              | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING      | <input type="checkbox"/> FINAL PRINTED LABELING        |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING       | <input checked="" type="checkbox"/> LABELING REVISION  |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION                 | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE   |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input checked="" type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW            |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA                    | <input type="checkbox"/> OTHER (SPECIFY BELOW):        |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT           |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |   |  |
|---|--|
| <input type="checkbox"/> DISSOLUTION            | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILTY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: See attached from the medical officer for this efficacy supplement, Dr. Maryann Gordon, for details regarding the consult request.

SIGNATURE OF REQUESTOR  
**Edward Fromm, CPMS, DCRP**

METHOD OF DELIVERY (Check one)  
 DFS       EMAIL       MAIL       HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

NDA 20845/S-017, IND #106,088  
Drug: INOMAX (nitric oxide gas)

(b) (4)

Supplement 017 dated 12-09-2014

The sponsor conducted study IK3001-BPD-301, the objective of which was to examine the efficacy of inhaled nitric oxide in preterm infants < 30 weeks gestational age with a birth weight < 1250 grams who required mechanical ventilation or positive pressure support on Days 5 to 14 after birth. The primary endpoint was survival without bronchopulmonary dysplasia (BPD) at 36 weeks. The study did not meet the primary endpoint.

The sponsor is proposing the following labeling revision based upon the outcome of this study:

(b) (4)

(b) (4)

We would like for you to review the study report and make recommendations, if any, for changing the product label.

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/s/  
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EDWARD J FROMM  
05/19/2015



NDA 20845/S-017

**ACKNOWLEDGEMENT --  
PRIOR APPROVAL SUPPLEMENT**

INO Therapeutics  
Attention: Peter Fernandes, M. Pharm  
Vice President, Regulatory Affairs  
Perryville III Corporate Park  
53 Frontage Rd., 3<sup>rd</sup> Floor, P.O. Box 9001  
Hampton, NJ 08827

Dear Dr. Fernandes:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA Number: 20845

Supplement Number: 017

Product Name: INOmax (nitric oxide) for inhalation, 100 ppm and 800 ppm

Date of Submission: December 9, 2014

Date of Receipt: December 11, 2014

This supplemental application proposes labeling revisions to include changes to the Highlights, Warnings and Precautions, and Clinical Studies sections of the INOmax package insert.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 9, 2015, in accordance with 21 CFR 314.101(a).

If the application is filed, the goal date will be October 11, 2015.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

## **FDAAA TITLE VIII RESPONSIBILITIES**

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505/351 of the FDCA/PHS Act, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, “Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank,” [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, “Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007,” that describes the Agency’s current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to NDA 20845/S-017 submitted on December 9, 2014, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

### **SUBMISSION REQUIREMENTS**

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Cardiovascular and Renal Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have questions, please call me at (301) 796-1072.

Sincerely,

*{See appended electronic signature page}*

Edward Fromm, R.Ph., RAC  
Chief, Project Management Staff  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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EDWARD J FROMM  
01/15/2015