CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20845

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

NITRIC OXIDE FOR INHALATION
(400 ppm in Nitrogen)

NDA 20-845

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
(HFD-110)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-845

NITRIC OXIDE FOR INHALATION

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new orphan drug application for Nitric Oxide for Inhalation, Ohmeda Pharmaceutical Products Division Inc (Ohmeda PPD), Liberty Corner, New Jersey 07938-0804 prepared an environmental assessment (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product. The format for the environmental assessment for an orphan drug NDA, defined in 21 CFR 25.31a (b) (3), is the same as the Tier 0 format.

The combustion of fossil fuels results in the emission of millions of tons of nitric oxide into the atmosphere. The quantities used for medical purposes are very small by comparison. Furthermore, precautions used in manufacturing and administration to patients are designed to minimize atmospheric emissions related to this NDA.

Nitric oxide is a synthetic gaseous drug substance. It is diluted in nitrogen, specifically, 400 ppm NO in nitrogen. It is administered to term and near term infants in conjunction with mechanical ventilation for the treatment of respiratory hypoxia. The drug substance, nitric oxide, and the drug product, Nitric Oxide for Inhalation, are manufactured, packaged, tested and labeled by BOC Gases, Port Allen, LA 70767. Both Ohmeda PPD and BOC Gases are operating divisions of The BOC Group Inc. Chemical waste is collected and shipped from Port Allen by to a licensed chemical waste disposal company. All facilities are certified to operate in accord with applicable environmental regulations.

The drug product, Nitric Oxide for Inhalation, will be used primarily in hospitals and secondarily, in ambulatory transport.

Nitric oxide must be administered through the I-NOvent (or equivalent) delivery device to minimize escape of nitrogen oxides into the environment. The amount of inhaled nitric oxide that is absorbed by a patient is variable, however some nitric oxide rapidly diffuses into the vascular bed where it induces vasodilatation and undergoes rapid inactivation by reaction with hemoglobin to produce methemoglobin and the nitrate and nitrite ions. Nitric oxide absorbed by the patient is not excreted into the environment.

Acid waste from the drug substance manufacturing operations is neutralized to pH 7, analyzed and disposed into the municipal storm sewers.

Residual nitric oxide (drug substance) contained in reusable aluminum alloy compressed gas cylinders with a stainless steel valve with Teflon O-Ring, is disposed by BOC Gases at the Port Allen site. The contents of compressed gas cylinders containing less than 10% nitric oxide may vented to the atmosphere according to the Small Source Exemption for Air Emission issued by the State of Louisiana to BOC Gases on December 14, 1994. Alternatively, the cylinders may be shipped to a licensed chemical waste disposal company. This includes all rejected, used (empty), unused (partially full) or expired drug product cylinders.

The contents of compressed gas cylinders containing more than 10% nitric oxide are treated with oxygen to form higher oxides of nitrogen, scrubbed with caustic solution and disposed by

Supplies not returned by American hospitals, pharmacies and clinics will be disposed according to their procedures.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the drug substance and the drug product are expected to minimize occupational exposures and environmental release.

Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

July 21, 1997
Date

/S/

PREPARED BY: Florian Zielinski, Review Chemist
Division of New Drug Chemistry I

7/21/97
Date

/S/

DIVISION CONCURRENCE: Robert Wolters
Division of New Drug Chemistry I

7/26/97
Date

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APPROVED: Nancy B. Sager, Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

Attachments: Environmental Assessment, pages 332 to 356
Material Safety Data Sheets
a) Nitric Oxide, pages 344 to 350
b) Nitric Oxide in Nitrogen, 0.00001% to 1%, pages 351 to 356

Original: NDA 20-845
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HFD-357 Docket File
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HFD-110 Division File
HFD-110 CSO, Zelda McDonald
HFD-110 Review Chemist, Florian Zielinski

1. **Date of preparation**

February 21, 1997.

2. **Name of Applicant/Petitioner**

Ohmeda Pharmaceutical Products Division (PPD) Inc
The BOC Group of Companies

3. **Address**

110 Allen Road
Liberty Corner, NJ 07938, USA

4. **Description of Proposed Action**

a. **Requested Approval**

Pursuant to section 505 (b)(2) of the Act, Ohmeda PPD is submitting an NDA for an orphan drug, I-NO™ (Nitric Oxide) for Inhalation, 400 ppm (in nitrogen), packaged in a seamless aluminum compressed gas cylinder with a stainless steel valve and Teflon gasket. An environmental assessment (EA), prepared according to the Tier 0 approach, is being submitted pursuant to 21 CFR 25.25a(b)(5) and the FDA EA guideline.

b. **Need For Action**

Approval for this orphan drug is sought for the treatment for respiratory hypoxia in conjunction with mechanical ventilation in term and near-term infants (≥ 34 weeks gestation), which may be caused by such conditions as persistent pulmonary hypertension, respiratory distress syndrome (RDS), meconium aspiration, pneumonia/sepsis, and congenital diaphragmatic hernia.[2] This is a new therapy for the

[2] The product is delivered *via* an approved ventilator system at a recommended

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