

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20845**

**CORRESPONDENCE**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Z. McDonald

Food and Drug Administration  
Rockville MD 20857

NDA 20-845

MAY 28 1999

INO Therapeutics, Inc.  
Attention: Richard N. Williams, Ph.D.  
54 Old Highway 22  
Clinton, NJ 08809

Dear Dr. Williams:

We have received your new drug application (NDA) resubmitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: INOmax (nitric oxide)

Therapeutic Classification: Priority (P)

Date of Resubmission: May 24, 1999

Date of Receipt: May 26, 1999

Our Reference Number: 20-845

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on July 25, 1999 in accordance with 21 CFR 314.101(a).

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Cardio-Renal Drug Products, HFD-110  
Attention: Division Document Room  
5600 Fishers Lane  
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Cardio-Renal Drug Products, HFD-110  
Attention: Division Document Room  
1451 Rockville Pike  
Rockville, Maryland 20852-1420

NDA 20-845

Page 2

If you have any questions, please contact:

Ms. Zelda McDonald  
Regulatory Health Project Manager  
(301) 594-5333

Sincerely yours,

Natalia A. Morgenstern  
Chief, Project Management Staff  
Division of Cardio-Renal Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

cc:

Archival NDA 20-845

HFD-110/Div. Files

DISTRICT OFFICE

HFD-110/Z. McDonald

sb/5/28/99

filename: 20845ac.doc

ACKNOWLEDGEMENT (AC)

McDonald

DEC 10 1997

NDA 20-845

Ohmeda Pharmaceutical Products Division Inc.  
Attention: Ms. Priya Jambhekar  
P.O. Box 804  
110 Allen Road  
Liberty Corner, NJ 07938-0804

Dear Ms. Jambhekar:

Please refer to your new drug application (NDA) for nitric oxide for inhalation, 400 ppm.

In reviewing your submission of June 16, 1997, our Medical Officer has raised a number of questions that require your attention. Our concerns with your submission are detailed as part of this correspondence (see enclosure).

Sincerely yours,

Natalia A. Morgenstern  
Chief, Project Management Staff  
Division of Cardio-Renal Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure

Dr. Throckmorton's 11/24/97 review, pgs 138-248

cc:

Original NDA

~~HFD-110~~

HFD-110/ZMcDonald/12/4/97

sb/12/8/97

GENERAL CORRESPONDENCE

McDonald

OCT 27 1997

NDA 20-845

Ohmeda Pharmaceutical Products Division Inc.  
Attention: Ms. Priya Jambhekar  
P.O. Box 804  
110 Allen Road  
Liberty Corner, NJ 07938-0804

Dear Ms. Jambhekar:

Please refer to your new drug application (NDA) for nitric oxide.

In reviewing your submission of June 16, 1997, our Pharmacologist has raised a number of questions that require your attention. Our comments on your submission are detailed as part of this correspondence (see enclosure).

Sincerely yours,

Natalia A. Morgenstern  
Chief, Project Management Staff  
Division of Cardio-Renal Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure

Dr. Oza's review dated October 10, 1997

cc:

Original NDA

HFD-110

HFD-110/ZMcDonald/10/21/97

sb/10/27/97

GENERAL CORRESPONDENCE



DEPARTMENT OF HEALTH & HUMAN SERVICES

Z. McDonald  
Public Health Service

Food and Drug Administration  
Rockville MD 20857

NDA 20-845

SEP 29 1997

Ohmeda Pharmaceutical Products Division Inc.  
Attention: Ms. Priya Jambhekar  
P.O. Box 804  
110 Allen Road  
Liberty Corner, NJ 07938-0804

Dear Ms. Jambhekar:

We acknowledge the receipt of your September 16, 1997 communication requesting withdrawal of your pending new drug application (NDA) for INOmax (nitric Oxide) for inhalation.

In compliance with your request and as provided under 21 CFR 314.65, the application is withdrawn as of the date of our receipt of your request for withdrawal, September 17, 1997. This withdrawal does not prejudice any future resubmission. You may request that the information contained in the withdrawn application be considered in conjunction with any resubmission.

Under section 736(a)(1)(A)(ii)(II) of the Prescription Drug User Fee Act of 1992 (PDUFA), the remaining 50% of the user fee is due upon withdrawal after filing of a pending application. If you decide to resubmit your application at a future time, under section 736(a)(1)(C) of the PDUFA, the submission will not be subject to a fee.

If you have any questions, please contact:

Ms. Zelda McDonald  
Regulatory Health Project Manager  
(301) 594-5333

Sincerely yours,

Natalia A. Morgenstern  
Chief, Project Management Staff  
Division of Cardio-Renal Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Z. McDonald

SEP 12 1997

NDA 20-845

Ohmeda Pharmaceutical Products Division Inc.  
Attention: Ms. Priya Jambhekar  
P.O. Box 804  
110 Allen Road  
Liberty Corner, NJ 07938-0804

Dear Ms. Jambhekar:

Please refer to your new drug application (NDA) for nitric oxide for inhalation, 400 ppm.

In reviewing your submission of June 16, 1997, our Medical Officer has raised a number of questions that require your attention. Our concerns with your submission are detailed as part of this correspondence (see enclosure).

Sincerely yours,

Natalia A. Morgenstern  
Chief, Project Management Staff  
Division of Cardio-Renal Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure

L. Miriam Pina, M.D.'s 8/25/97 review

cc:

Original NDA

~~HFD-110~~

~~HFD-110/ZMcDonald/9/9/97~~

~~sb/9/11/97~~

GENERAL CORRESPONDENCE



DEPARTMENT OF HEALTH & HUMAN SERVICES

Z. McDonald

Public Health Service

Food and Drug Administration  
Rockville MD 20857

NDA 20-845

JUN 19 1997

Ohmeda Pharmaceutical Products Division Inc.  
Attention: Ms. Priya Jambhekar  
P.O. Box 804  
110 Allen Road  
Liberty Corner, NJ 07938-0804

Dear Ms. Jambhekar:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: I-NO (nitric oxide)

Therapeutic Classification: P

Date of Application: June 16, 1997

Date of Receipt: June 16, 1997

Our Reference Number: NDA 20-845

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on August 12, 1997 in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102(c) of the new drug regulations and in accordance with the policy described in the Center for Drug Evaluation and Research Staff Manual Guide CDER 4820.6, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Please request the meeting at least 15 days in advance. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact:

Ms. Zeld McDonald  
Regulatory Health Project Manager  
(301) 594-5333



Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

Natalia A. Morgenstern  
Chief, Project Management Staff  
Division of Cardio-Renal Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

cc

Orig. NDA

HFD-110

DISTRICT OFFICE

HFD-110/ZMcDonald

sb/6/18/97

ACKNOWLEDGEMENT - AC

**OHMEDA**

THE BOC GROUP

Ohmeda Pharmaceutical Products Division Inc  
PO Box 804 / 110 Allen Road  
Liberty Corner NJ 07938 0804  
908 647 9200

June 10, 1997

Food and Drug Administration  
1451 Rockville Pike  
5th Floor  
Rockville MD 20852

VIA FAX

Attention: Raymond Lipicky, MD  
Director, Division of Cardio-Renal Drug Products

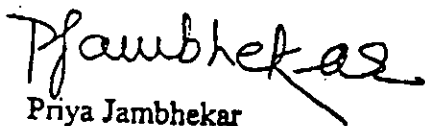
re: NDA 20-845, Nitric Oxide for Inhalation, 400 ppm  
Submission of a press release to announce NDA submission

Dear Dr. Lipicky,

Reference is made to a teleconference of June 4, 1997 between Ms Zelda McDonald of the Agency and Ohmeda Pharmaceutical Products Division Inc, (Ohmeda PPD). As discussed during the teleconference, Ohmeda PPD plans to submit the NDA on June 16, 1997 and would like to announce filing of this NDA immediately afterwards. A copy of the proposed press release is attached for your review.

Thank you very much in advance for prompt review of the proposed press release. Please call me at 908/604-7722 if you have any comments or questions regarding this press release.

Sincerely,



Priya Jambhekar  
Director, Regulatory Affairs

cc: Zelda McDonald  
Project Manager

enc: Proposed Press Release

EM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

IND

OCT 30 1996

Ohmeda Pharmaceutical Products Division, Inc.  
Attention: Mr. Christopher J. Schaber  
110 Allen Road  
Liberty Corner, NJ 07938-0804

Dear Mr. Schaber:

Please refer to your investigational new drug applications (INDs) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for nitric oxide.

We also refer to the Pre-NDA meeting held on September 27, 1996, between representatives of your firm and this Agency. The following represents our summary of the meeting.

Background:

Ohmeda has submitted INDs for the use of inhaled nitric oxide in the treatment of persistent pulmonary hypertension in the neonate (PPHN) and for Acute Respiratory Distress Syndrome (ARDS) under INDs respectively. At the same time Ohmeda was conducting their NO1 and NO2 studies, the National Institute of Child Health and Human Development (NICHD) was conducting the neonatal inhaled Nitric Oxide Study (NINOS). The NINOS was a randomized clinical trial using inhaled NO for term and near-term infants with hypoxic respiratory failure. The trial was stopped on May 2, 1996 on the recommendation of the Data Safety Monitoring Committee since the Committee had concluded that the study met the primary outcome without evidence of toxicity. Ohmeda subsequently stopped their studies on June 25, 1996 because they found they were unable to enroll patients with the NICHD study results known. Dr. Wright has agreed that the results of the NINOS may be referred to by FDA in support of the Ohmeda application for nitric oxide in PPHN. The purpose of this meeting was to discuss the preparation of an NDA for the use of nitric oxide in the treatment of persistent pulmonary hypertension in the neonate.

Discussion Points/Decisions/Agreements Reached:

1. Does the content of the clinical section, as outlined below, remain acceptable to the Agency in support of the neonatal NDA?

Inhaled NO 01 and 02 Studies-	Full Clinical Report
NINOS -	Manuscript (as recommended by FDA)
Wessel Study-	Manuscript/Abbreviated Clinical Report
Roberts Study-	Manuscript/Abbreviated Clinical Report
Inhaled NO 04 and 05 Studies-	Full Clinical Report
Inhaled NO Literature Review-	Reports/Summaries on 1) other neonatal studies and 2) non-neonatal studies

- The above outline is acceptable to the Agency. (Studies 04 and 05 are not needed for this NDA, see item #4 below.)

With regard to the NINOS study, the Division requested that the following be submitted to the NINOS IND:

- Full data tape with SAS variables.
- Annotated case report forms.
- The manuscript that was submitted to the New England Journal of Medicine for publication.
- The original protocol and dated set of amendments.
- Accounting of all patients, i.e., all numbers should add up.

The Division requested that Ohmeda's NDA contain the following with regard to the NO 01 and 02 studies:

- Full data tape with SAS variables.
- Annotated case report forms.
- Clinical report should consist of the original protocol, dated set of amendments and an analysis of the results.
- Accounting of all patients, i.e., all numbers should add up.
- Tabular listing need not be included.

2. Is it necessary for Ohmeda to have three month stability data on nitric oxide in their to-be-marketed cylinders at the time the NDA is submitted?
  - The Division agreed it would not be necessary.
3. A strategy for defending the data from NINOS before an Advisory Committee since Ohmeda will have limited access to the predefined summary tables. Ohmeda may be unable to answer questions concerning "interesting" subgroups or trends that arise from close scrutiny of the data by FDA.
  - Dr. Wright agreed that one of the principal investigators from NINOS would present NINOS before the Advisory Committee.
  - The Division believed that there was a high probability the application would be taken before the Advisory Committee.
4. The possibility of providing the interim study report for Ohmeda's completed phase II ARDS trials (protocols 04 and 05) in the neonatal NDA, in lieu of a full clinical report (containing safety data only).
  - The Division concluded that the ARDS protocols 04 and 05 would not be needed for the PPHN NDA, therefore, the interim report would not be needed.

5. The content and preparation of the integrated summaries of efficacy and safety.
  - The Division believed that an integrated summary of efficacy would not be needed, but some sort of integrated summary of safety would be needed.
  - The firm asked if they could meet with the Division again to discuss a strategy for writing an integrated summary of safety, and the Division agreed.
  
6. The practical issues in attempting to satisfy the August 23, 1996 FDA letter wherein the Agency strongly suggested that every effort be made to achieve a 0% loss-to-follow-up rate for protocols 01 and 02 (N=153).
  - The Division encouraged the firm to be aggressive in locating all patients treated under studies 01 and 02 and obtaining follow-up data on them. The Division believed the firm would not have to have all the long term outcomes at the time the NDA is submitted but a decision would not be made until those data are submitted. If the application is a "P," the firm should be diligent in submitting the follow-up data since there will be only a six month window to action. If the data are not submitted on time, it is possible the Agency would issue a not approvable letter. Although it is not the Division's intention to take an action until the follow-up data are reviewed, if the data are strikingly convincing, it is possible the application could be approved without long-term data.
  
7. The NIH will be issuing a "Clinical Alert" regarding the results of NINOS. Does the Division wish to be involved in writing the clinical alert? Because of the Clinical Alert, Ohmeda expects that there will be many more new investigators, especially from primary care hospitals, requesting use of NO who may not be as qualified as earlier investigators from tertiary care hospitals. How will the Agency handle such investigators?
  - The Division would like to be involved in the writing of the clinical alert.
  - The new investigators can obtain their own IND or they can become investigators under either Ohmeda's IND or the NINOS IND. The Division expressed concern that the Clinical Alert will trigger many new IND requests from clinicians who may be underinformed about necessary procedures and precautions for

use of nitric oxide. Meeting participants agreed that it may be useful for NIH to refer, in the Clinical Alert, to some sort of instruction sheet to be devised and provided to would-be IND holders.

If you have any questions concerning these INDs, please contact:

Ms. Zelda McDonald  
Regulatory Health Project Manager  
(301) 594-5333

Sincerely yours,

Natalia A. Morgenstern  
Chief, Project Management Staff  
Division of Cardio-Renal Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

cc:

Original IND

HFD-110

HFD-110/ZMcDonald/10/24/96

sb/10/29796

GENERAL CORRESPONDENCE



THE BOC GROUP

Pharmaceutical Products Division

Ohmeda Inc  
110 Allen Road PO Box 804  
Liberty Corner NJ 07938 0804  
908 647 9200

October 5, 1994

Food and Drug Administration  
HFD-110, Room 16B-45  
5600 Fishers Lane  
Rockville MD 20857

Attention: Raymond Lipicky, MD  
Director, Division of Cardio-Renal Drug Products

DESK COPY

re: IND  
Inhaled Nitric Oxide (INO)  
Serial #032 - General Correspondence

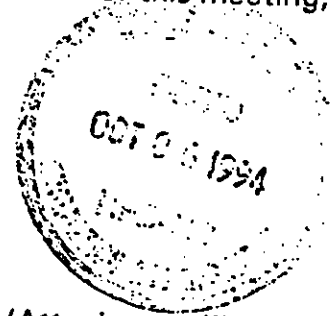
Dr Cunningham

Dear Dr Lipicky:

We refer to the upcoming meeting scheduled for October 18, 1994 at 10:00 am, between the FDA reviewing chemist and representatives of our company, to discuss key CMC features of the Inhaled Nitric Oxide (INO) IND towards preparation of an NDA.

We thank you for your time in meeting with us. As preparation for this meeting, the following background information is attached:

- Proposed Meeting Agenda/Attendees
- Drug Substance Profile (Attachment I)
- Drug Product Profile (Attachment II)
- Drug Substance/Product Analytical Controls (Attachment III)
- Drug Substance/Product Stability (Attachment IV)
- Environmental Assessment (Attachment V)



Raymond Lipicky, MD  
October 5, 1994  
Page 2

If you have any questions prior to the meeting, please contact me at  
(908) 604-7704 or Steven Pikulin at (908) 604-7703.

Sincerely Yours,

*Steven Pikulin* FOR

Robert I. Outwater  
Senior Director, Worldwide Regulatory Affairs

Desk Copies:

Dr Wolters  
Dr Cunningham

enc: Form FDA 1571

SP:ab



**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
INVESTIGATIONAL NEW DRUG APPLICATION (IND)  
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) Part 312)**

Form Approved: OMB No. 0910-0014.  
Expiration Date: November 30, 1995.  
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40)

1. NAME OF SPONSOR Ohmeda Pharmaceutical Products Division Inc	2. DATE OF SUBMISSION October 5, 1994
3. ADDRESS (Number, Street, City, State and Zip Code) 110 Allen Road Liberty Corner NJ 07938 0804	4. TELEPHONE NUMBER (Include Area Code) 908/604-7704

5. NAME(S) OF DRUG (include all available names: Trade, Generic, Chemical, Code) Nitric oxide	6. IND NUMBER (if previously assigned)
--	--

7. INDICATION(S) (Covered by this submission)  
Persistent Pulmonary Hypertension in the Newborn (PPHN) and Acute Respiratory Distress Syndrome (ARDS)

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED:  PHASE 1  PHASE 2  PHASE 3  OTHER \_\_\_\_\_ (Specify)

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), DRUG MASTER FILES (21 CFR 314.420), AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION.

10. IND submissions should be consecutively numbered. The initial IND should be numbered "Serial Number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.	SERIAL NUMBER: <u>0</u> <u>3</u> <u>2</u>
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11. THIS SUBMISSION CONTAINS THE FOLLOWING: (Check all that apply)

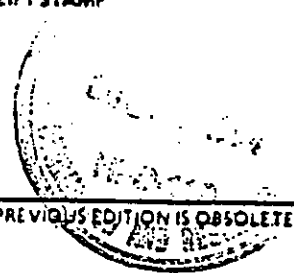
<input type="checkbox"/> INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)	<input type="checkbox"/> RESPONSE TO CLINICAL HOLD
PROTOCOL AMENDMENT(S):	IND SAFETY REPORT(S):
<input type="checkbox"/> NEW PROTOCOL	<input type="checkbox"/> INITIAL WRITTEN REPORT
<input type="checkbox"/> CHANGE IN PROTOCOL	<input type="checkbox"/> FOLLOW-UP TO A WRITTEN REPORT
<input type="checkbox"/> NEW INVESTIGATOR	
<input type="checkbox"/> RESPONSE TO FDA REQUEST FOR INFORMATION	<input type="checkbox"/> ANNUAL REPORT
<input type="checkbox"/> REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED.	<input checked="" type="checkbox"/> GENERAL CORRESPONDENCE
	<input type="checkbox"/> OTHER _____ (Specify)

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

TREATMENT IND 21 CFR 312.35(b)  TREATMENT PROTOCOL 21 CFR 312.35(b)  CHANGE REQUEST NOTIFICATION 21 CFR 312.71(d)

FOR FDA USE ONLY	
COR/DBIND/OGD RECEIPT STAMP	DDR RECEIPT STAMP
	IND NUMBER ASSIGNED:
	DIVISION ASSIGNMENT:





THE BOC GROUP

Ohmeda Pharmaceutical Products Division Inc  
PO Box 804 / 110 Allen Road  
Liberty Corner NJ 07938 0804  
908 647 9200

Ms. Priya Jambhekar  
Director, Regulatory Affairs  
Ohmeda Pharmaceutical Products Division Inc.  
110 Allen Road  
Liberty Corner, New Jersey 07938-0804

June 10, 1997

Re: Patent Certification - I-NO™ (Nitric Oxide)  
Ohmeda Pharmaceutical Products Division Inc.  
Our Ref. PA# 10

Dear Ms. Jambhekar:

This is to certify that Ohmeda Pharmaceutical Products Division Inc. is the exclusive licensee for the rights to the administration of Nitric Oxide by inhalation for the prevention and treatment of reversible pulmonary vasoconstriction. These rights were acquired from the General Hospital Corporation of Boston, Massachusetts under the following U.S. Patent:

U.S. Patent No. 5,485,827 which claims prevention or treatment of reversible pulmonary vasoconstriction by the inhalation of nitric oxide with an oxygen-containing gas. This patent expires January 23, 2013.

If you require additional information with regard to the U.S. patent discussed herein, please so advise me.

Very truly yours,

R. Hain Swope  
Patent Counsel

0079 01