CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20845

ADMINISTRATIVE DOCUMENTS

RHPM Overview of NDA 20-845
INOmax (nitric oxide) Inhaled
Update November 14, 1999

Type: 1P
Receipt Date: May 26, 1999
User Fee Goal Date: November 26, 1999
Approvable Letter Issued: November 19, 1999

Background
Ohmeda originally submitted this application on June 16, 1997 for the use of nitric oxide in the treatment of hypoxic respiratory failure of the newborn. Orphan Drug designation was granted for this use on June 13, 1993. The application was withdrawn on September 17, 1997 before an action was taken. There have been two Advisory Committee meetings, one before the application was submitted (August 28, 1995) and the other after the application was withdrawn (April 9, 1998).
INO Therapeutics. Inc. acquired the NDA and resubmitted the application on May 26, 1999

Medical Reviews
There were two medical reviews of the NINOS and INO-01/02 trials completed during the first review period:

In his review dated November 24, 1997, Dr. Throckmorton, Medical Officer, HFD-110, recommended that the application not be approved stating that there was not sufficient data suggesting a clear beneficial effect of I-NO on hard endpoints. This was coupled with the potential adverse events associated with I-NO administration and the inadequacy of the safety database for certain key adverse events.

In her review dated August 25, 1197, Dr. Pina, Medical Officer, HFD-570, stated that there were many outstanding issues that prevent us from recommending these trials as supportive of the safety and efficacy of NO for the treatment of hypoxic respiratory failure. See her review.

There was one medical review of the CINRGI trial during the second review period:

In his review dated October 29, 1999, Dr. Throckmorton concluded that beyond the statistically significant findings of improvement in oxygenation and decreased ECMO, no effect of I-NO on durable clinical efficacy (duration of hospitalization, neurologic status at discharge) was demonstrated. There was a trend towards less evidence of pulmonary injury at the time of discharge that is complicated by the baseline imbalance in pulmonary status. Using incomplete follow-up data through one year, no adverse or beneficial effects of I-NO on mortality of neurologic/pulmonary status were identified, again relative to the control group. He recommended approval with careful labeling to reflect limits of the data.

Medical Team Leader Memo
In his draft review, Dr. Stockbridge provided two options: 1) Not approve the application because of inadequacies in the design and implementation of the major studies and the lack of demonstrated long-term benefit. Doing so, however, would not likely create and environment wherein a better placebo-controlled study would be forthcoming. 2) Approve the use of nitric oxide with a label suitably circumspect with regard to the potential benefits and risks. Per Dr. Stockbridge, a safety update was not needed because all studies were completed before the application was submitted.

Statistical Review
In his review dated November 4, 1999, Dr. Cui came to essentially the same conclusions as the medical reviewer.

Pharmacology
In his review dated October 9, 1997, Dr. Oza was unable to completely assure safety because NO toxicity mechanisms are not known and the data did not prove beyond a reasonable doubt that NO can be administered at a safe dose that does not for methemoglobin. If the clinical data suggested distinct

benefits, he favored the use of a very low dose. The dose should never exceed 10 ppm. There is support from the animal data on the efficacy for the low dose although risk cannot be excluded.

Biopharmaceutical Review
In her review dated November 10, 1999, Dr. Nguyen states that the application does not completely fulfill the requirement of the Office of Clinical Pharmacology and Biopharmaceutics since the pharmacokinetic information in the target population was not submitted. The labeling should clearly state that the uptake, distribution and elimination were determined primarily in healthy adults.

Clinical Inspection
In his clinical inspection summary dated September 22, 1999, Dr. U stated that the data collected from the three sites can be used in support of the NDA claim.

Chemistry Review
In his review dated November 5, 1999, Dr. Advani stated that the NDA may be approved from a chemistry viewpoint. The action letter should state that the expiry date is 30 months for a drug product stored at 25^0 C. Container labels need to be provided.

Trade Name:
The trade name, INOmax, was found acceptable by the Labeling and Nomenclature Committee on November 3, 1997.

Establishment Inspection:
The establishment inspection was recommended acceptable on October 22, 1999.

Methods Validation:
The firm has submitted the validation package. It will be sent to our district laboratories for evaluation.

Environmental Assessment:
Nitric Oxide was found to have no significant impact on the environment on July 26, 1997.

DDMAC
The firm submitted promotional material, received December 9, 1999. DDMAC is reviewing it.

Cardiac and Renal Drugs Advisory Committee
There was no Advisory Committee held specifically for this application.

CSO Summary

Final printed labeling was received December 9, 1999 that incorporated all labeling recommendations in the NDA Action Letter Routing Record and the marked-up labeling that accompanied the approvable letter. To my knowledge, there are no issues that would prevent action on this application.

An approval letter will be drafted for Dr. Temple's signature.

/S/
Zelda McDonald, RHPM

cc: Orig. NDA
HFD-110
HFD-111/McDonald

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Medical Team Leader Memo He recommended approval with careful labeling to reflect limits of data

Deputy Division Director Memo
In his draft review, Dr. Stockbridge provided two options: 1) Not approve the application because of inadequacies in the design and implementation of the major studies and the lack of demonstrated long-term benefit. Doing so, however, would not likely create and environment wherein a better placebo-controlled study would be forthcoming. 2) Approve the use of nitric oxide with a label suitably circumspect with regard to the potential benefits and risks. Per Dr. Stockbridge, no safety update was needed because all of the studies were completed before the submission - CL 11/22/99

Statistical Review
In his review dated November 4, 1999, Dr. Cui came to essentially the same conclusions as the medical reviewer.

Pharmacology
In his review dated October 9, 1997, Dr. Oza was unable to completely assure safety because NO toxicity mechanisms are not known and the data did not prove beyond a reasonable doubt that NO can be administered at a safe dose that does not for methemoglobin. If the clinical data suggested distinct benefits, he favored the use of a very low dose. The dose should never exceed 10 ppm. there is support from the animal data on the efficacy for the low dose although risk cannot be excluded.

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Environmental Assessment:
Nitric Oxide was found to have no significant impact on the environment on July 26, 1997.

Cardiac and Renal Drugs Advisory Committee
There was no Advisory Committee held specifically for this application.

CSO Summary
An approvable letter will be drafted for Dr. Temple.

The marked-up labeling in this package contains changes from all disciplines except Biopharm. I have requested container labeling from the firm.

To my knowledge, there are no issues that would prevent action on the goal date, November 26, 1999.

/S/
Zelda McDonald, RHPM

cc: Orig. NDA
HFD-110

RHPM Review of Final Printed Labeling
NDA 20-845

Date of Submission:	December 8, 1999
Date of Review:	December 13, 1999
Applicant Name:	INO Therapeutics
Product Name:	INOmax (nitric oxide) 100 and 800 ppm for Inhalation

Evaluation:
This submission provides for final printed labeling in accordance with our approvable letter dated November 19, 1999.

Recommendation:
Except for a few minor editorial corrections, the labeling is identical in content to the marked-up labeling that accompanied the approvable letter (November 19,1999) and the fax containing pharm/tox labeling additions dated November 22, 1999.

An approval letter should issue for this application.

/S/
Zelda McDonald, RHPM

cc: orig. NDA
HFD-110
HFD-110/McDonald
HFD-110/Blount
HF-2

Z. McDonald

RECORD OF TELEPHONE CONVERSATION

SEP 11 1997

Date: September 9, 1997
Requested: September 8, 1997
NDA# 20-845
Product: Nitric Oxide
Sponsor: Ohmeda PPD
Contact: Ms. Priya Jambhekar
Phone#: 908-604-7722

Telecon Chair: Raymond Lipicky, M.D.
Telecon Recorder: Zelda McDonald
External Participant Lead: Priya Jambhekar

FDA Participants:
Raymond Lipicky, M.D. Director, Div. Cardio-Renal Drug Products, HFD-110
Douglas Throckmorton, M.D. Medical Officer, HFD-110
Zelda McDonald RHPM, HFD-110

Ohmeda Participants:
John Towse, Ph.D. Senior Director of Clinical and Regulatory Development
Priya Jambhekar Director, Regulatory Affairs, Ohmeda PPD

Background:
Ohmeda submitted an NDA on June 16, 1997 for the use of inhaled nitric oxide in the treatment of persistent pulmonary hypertension in the neonate (PPHN). Ohmeda is scheduled to present inhaled nitric oxide at the Cardiac and Renal Advisory Committee (CRAC) meeting scheduled for October 23, 1997. Ohmeda requested this teleconference to discuss new safety information that has become available from a European trial.

Telecon:
Ohmeda stated that in the past couple of days, new safety data have surfaced from a European study of use of nitric oxide in 268 Adult Respiratory Distress Syndrome (ARDS) patients. At present, Ohmeda did not have the details but expected to by next week and requested a meeting with the Division and Dr. Temple (next week) to discuss these new data in light of the nitric oxide development program and the upcoming advisory committee meeting. Ohmeda was concerned because the new study showed a higher number of deaths in the nitric oxide group versus the placebo group. Since Ohmeda had received an indication from the Division that there was a safety concern with the PPHN application, they wished to present the data to the Division and discuss the impact the new data may have on the advisory committee.

- The Division believed that the new data were not pertinent since Ohmeda's current NDA application was for use in neonates not adults. The Division advised Ohmeda to spend their efforts on putting their presentation for the advisory committee meeting into good shape instead of worrying about data from a trial they do not know much about. The Division did not believe it was necessary for Ohmeda to meet with the Division to make a formal presentation of a trial that is not well documented, that is not in a population of

interest and that does not have the pathophysiology of patients of interest. Whether to meet would be Ohmeda's call, however. The Division believed Ohmeda would be better off spending their time doing a meta analysis of deaths in the PPHN controlled trials to show that the safety issues were not significant. Mortality data from other studies in PPHN and neonates would also help address the issue of the increased number of deaths. Ohmeda should be knowledgeable about the safety information in ARDS, but noted that ARDS is not what the advisory committee will be dealing with.

Ohmeda believed that the data from the new ARDS study put a different inflection on their program and stated that the President of their Division wondered whether Ohmeda should withdraw the NDA.

- The Division stated that the Division would not give advice as to whether the NDA should be withdrawn. The Division believed the best thing to do would be to present nitric oxide before the advisory committee. Both Ohmeda and the Division know that the nitric oxide data base is weak, however, Ohmeda's efforts ought to go toward making a compelling case that nitric oxide is a therapy for PPHN.

Signature, telecon recorder: /S/ 9/11/97

Concurrence, Chair: /S/ 9/12/97

cc: Orig. IND
~~HFD-110~~
HFD-111/McDonald
Drafted: 9/10/97 Finaled: 9/11/97
Throckmorton 9/10/97

13.0 PATENT INFORMATION (21 CFR 314.53)

Pursuant to 505(b) of the FD &C Act and 21 CFR 314.50, the following information is provided on the patent(s) that apply to the New Drug Application (NDA) for nitric oxide gas for inhalation. The information is limited to the drug substance, drug product (formulation and composition) and method of use patents. Information on process patents (if any) is not included in this section.

13.1 PATENT NUMBER AND EXPIRATION DATE

13.1.1 Patent Number

U. S. Patent 5,485,827

13.1.2 Patent Expiration date

January 23, 2013

13.2 TYPE OF PATENT

The above mentioned patent is a method of use patent for prevention or treatment of reversible pulmonary vasoconstriction by the inhalation of nitric oxide with an oxygen containing gas.

13.3 NAME OF THE PATENT OWNER

The patent is owned by General Hospital Corporation of Boston, Massachusetts. Ohmeda PPD acquired rights to this patent from the patent owner.

EXCLUSIVITY SUMMARY FOR NDA # _20-845_____ SUPPL #_____

Trade Name __I-NOmax_____ Generic Name _nitric oxide_____

Applicant Name _INO Therapeutics, Inc._____ HFD # __110_____

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it an original NDA?

YES /_X__/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /_X__/

If yes, what type? (SE1, SE2, etc.) _____

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 /_X__/ NO /___/

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:

_____

_____

Form OGD-011347 Revised 10/13/98

cc: Original NDA Division File HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /_X__/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?
7 years – Orphan status granted on June 22, 1993

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

_____No_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /_X_/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 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 /_X__/

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

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

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. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S 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:

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"):

_____ _____

_____ _____

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 # _____ 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 /___/ Explain _____ ! NO /___/ Explain _____

!

_____ ! _____

!

_____ ! _____

!

!

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: _____

_____

/S/ 8/10/99

Signature Date

Title: Regulatory Heatlh Project Manager

/S/ 11/23/99

Signature of Office/ Date

Division Director

cc: Original NDA Division File HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at time of the last action.

(NDA)/BLA # 20-845 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-110 Trade and generic names/dosage form: INOmax (nitric Oxide) Gas Action: AP AE NA

Applicant INO Therapeutics Therapeutic Class 1P

Indication(s) previously approved None

Pediatric information in labeling of approved indication(s) is adequate ✓ inadequate ___

Indication proposed in this application Persistant Pulmonary Hypertension of the newborn

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) ___No (Sign and return the form)

IN WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

__Neonates (Birth-1month) __Infants (1month-2yrs) __Children (2-12yrs) __Adolecents(12-16yrs)

__1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

__2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

__3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

- __a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- __b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
- __c. The applicant has committed to doing such studies as will be required.
  - __ (1) Studies are ongoing,
  - __ (2) Protocols were submitted and approved.
  - __ (3) Protocols were submitted and are under review.
  - __ (4) If no protocol has been submitted, attach memo describing status of discussions.
- __d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

__4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

__5. **If none of the above apply,** attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE 4 COMMITMENTS IN THE ACTION LETTER? ___ Yes ___No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from medical review (e.g., medical review, medical officer, team leader)

/S/

Signature of Preparer and Title

Date 11/1/99

cc: Orig (NDA)/BLA # 20-845
HFD-110 /Div File
NDA/BLA Action Package
HFD-~~806/KRoberts~~ /Crescenzi

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM, CONTACT KHYATI ROBERTS, HFD-6 (ROBERTSK)

NDA 20-845, NITRIC OXIDE FOR INHALATION
NEW DRUG APPLICATION

DEBARMENT/CONVICTION CERTIFICATION

In accordance with the requirement of the Federal Food, Drug, and Cosmetic Act, INO Therapeutics, Inc. hereby certifies that it did not and will not use, in any capacity, the services of any person debarred by the Food and Drug Administration (FDA).

Furthermore, INO Therapeutics, Inc. certifies that neither the applicant nor any affiliated persons responsible for the development or submission of the application has been debarred by the FDA.

R N Williams

Richard N. Williams, Ph.D.
Vice President
Worldwide Regulatory Affairs

Date: Nov. 18, 1999

MEMORANDUM

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

DATE: NOV 19 1999

FROM: Robert Temple, M.D.
Director, Office of Drug Evaluation I, HFD-101

SUBJECT: INOmax (Nitric Oxide, INO Therapeutics, NDA 20-845)

TO: Raymond J. Lipicky, M.D.
Director, Division of Cardio-Renal Drug Products, HFD-110
File NDA 20-845

Both Drs. Stockbridge and Throckmorton have recommended approval of inhaled NO for the treatment of hypoxic respiratory failure (of various causes) in neonates, with close attention in labeling to what it does [improve pAO_2 and decrease need for extra-corporeal membrane oxidation (ECMO)] and does not (alter survival, preserve neurologic function) do.

The evidence of effectiveness comes predominantly from two double-blind (but INO treated patients "pink" quickly, so that blinding is suspect), randomized trials in which need for ECMO or death plus need for ECMO were the primary endpoints. Table 1 summarizes the evidence. The ECMO endpoint has been the subject of some debate (is it a clinically meaningful endpoint?). Dr. Stockbridge says: "Avoidance of ECMO is a legitimate clinical benefit. While not associated with the degree of mortal or morbid risks it once had, the process remains risky and it is not universally available." Dr. Throckmorton (October 29, 1999 review, page 5), in his overall summary says that there is no evidence of a favorable effect of INO on "hard endpoints (death, hospitalization, days of ventilation, incidence of chronic lung disease or neurological sequelae)" and that "a clear clinical benefit . . . has not been demonstrated." But he doesn't quite mean that because he also says that "the beneficial effect of INO on the physiology of these severely ill patients (improvement in oxygenation) has been demonstrated. This effect allows for a decreased rate of use of an invasive and potentially dangerous procedure (ECMO)." He also makes the point that this sort of benefit should be achieved with little risk, and finds available data on this reassuring. Finally, Dr. Robert Meyer, Director Division of Pulmonary Drug Products) expresses skepticism (memorandum dated November 12, 1999) about the endpoint, noting that DPADP has asked for "tangible, clinically meaningful endpoints." He doesn't specifically explain why decreased ECMO is not such a benefit, except perhaps by noting that the "need" for ECMO may be based wholly on the extent of hypo-oxygenation, so that decreased ECMO is just a reflection of the increased oxygenation we always knew INO could provide but did not accept as adequate evidence of effectiveness. That may well be true, but it seems equally true that poor oxygenation will always be an important component of a decision to use ECMO, so that our quandary is simply unavoidable. If ECMO is something good to avoid, however, the stimulus to it may not matter.

All who have addressed this find it a close case, but I believe a clear decrease in use of ECMO, accompanied by evidence that INO is safe when used properly, should be considered a tangible benefit. Moreover, as I will explain, there may be no basis for expecting a benefit of INO except to spare ECMO, at least at sites where ECMO is available. So far as we know, INO does not reverse the injury or developmental abnormality that leads to hypoxic respiratory failure. It improves oxygenation of blood, probably by directing pulmonary blood flow to ventilated areas and by decreasing R to L shunting. This allows the neonate to maintain adequate oxygenation while the lesion is treated or outgrown. ECMO has the same intent; it is not itself a healing intervention; but prevents damage by maintaining an adequately oxygenated child while the patient improves. Rather it maintains an adequate oxygenated child. If this is

correct, i.e., if oxygenation by either method is to allow recovery, rather than to induce recovery, then INO probably can never be better than ECMO; it can only substitute for it and be as good at maintaining survival, neurological function, etc. We know ECMO can affect survival; decreasing use of ECMO without lowering survival is all INO can possibly do. But that seems a worthwhile benefit, so long as there are no serious adverse consequences. In fact, as Dr. Throckmorton explains in detail, there do not seem to be any. Moreover, in one study (CINRGI) there is a fairly substantial decrease in the rate of chronic lung disease in INO treated patients [11/82 (13%) vs. 3/92 (3%), p=0.023]. That finding may not be replicated and "claimable" but it's very reassuring. In both studies mortality is slightly less in the INO group, although an adverse trend had been seen in an earlier study.

I have marked up labeling some, but have a few specific questions.

1. If doses above 20 ppm do not increase oxygenation in non-responders to 20 ppm and lead to methemoglobinemia, why do we not discourage them strongly?

2. Is there any evidence other than CINRGI related to the occurrence of chronic lung disease? The finding in that study seems pretty strong.

3. Why are ADR's derived only from CINGRI study:

4. Why doesn't the Indication require both hypoxic respiratory failure and evidence of pulmonary hypertension (that was needed for entry into trials). Also, should hypoxia be defined?

/S/

Robert Temple, M.D.

cc:
Orig. NDA 20-845
HFD-110
HFD-570/R Meyer
HFD-110/N Stockbridge
HFD-110/D Throckmorton
HFD-110/Z McDonald
HFD-101/R Temple
drafted:sb/11/18/99
final:sb/11/19/99
filename:NitricOxideMM991118.doc

Table 1

Study	n Control	NO	Death Control	NO	Need ECMO Control	NO	Death or ECMO Control	NO	Chronic Lung Disease Control	NO
NINOS	121	114	20 (17%)	16 (14%) p=0.6	66 (55%)	44 (39%) p=0.014	77 (64%)	52 (46%) p=0.006	14 (14%)	16 (16%) p=0.71
CINRGI	89	97	5 (6%)	3 (3%) p=0.48	51 (57%)	30 (31%) p<0.001	52 (58%)	32 (33%) p<0.001	11 (13%)	3 (3%) p=0.023
INO 01/02	41	114	2 (5%)	10 (9%)	(22%)	(34%)	39%	(29%) NS		

All trials show acute (30 minutes) improvement in oxygenation after INO.

861

REQUEST FOR TRADEMARK REVIEW

TO: CDER Labeling and Nomenclature Committee
Attention: Dan Boring, R.Ph., Ph.D. HFD-530
9201 Corporate Blvd. Rm N 461

FROM: Division of: Cardio-Renal Drug Products HFD-110
Attention: Robert Wolters Phone: 594-5376

DATE: August 18, 1997

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Proprietary Name: I-NO NDA/ANDA 20-845
Note "I" is the letter="I" not number "1"
Note Ohmeda has withdrawn INO and request that we evaluate INOmax.

Trademark status: Yes X No Pending

Company Name: Ohmeda Pharmaceutical Products

Other proprietary names by the same firm for companion products:
None
Established name including dosage form and strength: Have not applied for an USAN name.
Gas 100 & 800 ppm in nitrogen

Indications for use including dosing schedule (may be a summary if proposed statement is lengthy):
Pulmonary hypertension in term and near term infants.

Comments from the submitter: (concerns, observations, etc.)

I-NO stands for inhaled nitric oxide

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev. Dec.96

Consult #861 (HFD-110)

INOmax

No USAN available

There were no look-alike/sound-alike conflicts noted or misleading aspects found in the proposed proprietary name.

The Committee finds the proposed proprietary name acceptable.

D Boring 11/3/97, Chair
CDER Labeling and Nomenclature Committee

Minutes of a Meeting

MAY 22 1998

Meeting Date: May 6, 1998
Our request

NDA: 20-845 IN-0 (nitric oxide)- Currently Withdrawn
INDs: [redacted]

External Participant: Ohmeda PPD

Type of Meeting: Guidance

Meeting Chair: Raymond Lipicky, M.D.
Meeting Recorder: Zelda McDonald
External Participant Lead: Priya Jambhekar

FDA Participants:

Raymond Lipicky, M.D.	Director, Div. of Cardio-Renal Drug Products, HFD-110
Martin Himmel, M.D.	Team Leader, Medical, HFD-570
Robert Fenichel, Ph.D., M.D.	Team Leader, Medical, HFD-110
Norman Stockbridge, M.D.	Team Leader, HFD-110
Douglas Throckmorton, M.D.	Medical Officer, HFD-110
Walid Nuri, Ph.D.	Statistician, HFD-710
Narendra Oza, Ph.D.	Pharmacologist, HFD-110
Florian Zielinski, Ph.D.	Chemist, HFD-810
Michael Bazaral, M.D.	Medical Officer, CDRH, HFZ-450
Zelda McDonald	RHPM, HFD-110

Ohmeda Participants:

Priya Jambhekar	Director, Regulatory Affairs, Ohmeda PPD
Richard Straube, M.D.	Director, Clinical Investigations Inhaled Nitric Oxide
Ashleigh Palmer	Program Director
Jerard Rhines	Project Manager, Inhaled Nitric Oxide
Frank Sasinowski, Esq.	Consultant Attorney

Background:

The Cardiovascular and Renal Drugs Advisory Committee met in open discussion on April 9, 1998 to review the systemic studies conducted on inhaled nitric oxide (INO) and to consider what is known about the safety and effectiveness of INO in Adult Respiratory Syndrome (ARDS) and in neonates with hypoxic respiratory failure. Ohmeda Pharmaceutical Products Division Inc. and individual investigators presented data from their studies to facilitate this review. Since no NDA for this product is currently filed, the committee did not review the integrity of the data presented. The committee was not able to determine consistent effects on pulmonary vascular resistance or systemic oxygenation that were predictive of clinical outcome in adults or neonates. They did find data on initiation of extracorporeal membrane oxygenation (ECMO) persuasive with respect to a decrease in death in neonates and that studies on administration of INO to neonates suggested oxygenation was improved and use of ECMO was reduced or delayed. They recommended that additional studies need to be conducted in both adults and neonates. No benefit on outcome for ARDS was demonstrated in any of the INO studies that

had been conducted. Studies in neonates were also inconclusive. Future studies in infants should not exclude concomitant use of such other techniques as use of surfactants and high-frequency oscillatory ventilation. Current policies with respect to proliferation of single center IND's should be reviewed. If the Agency determines that these policies make the conduct of controlled clinical trials difficult, then a more disciplined and controlled policy should be enforced for IND holders. The purpose of this meeting was to discuss how to proceed with nitric oxide development.

Discussion Points/Agreements Reached:

Ohmeda PPD (Ohmeda) stated that BOC, Ohmeda PPD's parent company, has sold Ohmeda PPD to Baxter. Ohmeda MSD (Devices) was sold to Datex Instramentarium and Ohmeda MDD (Diagnostics) was sold to Becton Dickinsen. The nitric oxide project, however, was not part of the sale to Baxter but was set aside as a joint venture by Datex and Becton Dickinson in a separate company called INO Holding Inc. in the hopes of selling it to one of several buyers who deal in medical gases. All the prospective buyers attended the Advisory Committee Meeting. After the meeting, all declined to buy it, because they did not get a sense, from committee discussion, of an acceptable, clear development plan. INO Holding Inc. has directed Ohmeda PPD to close out development of INO in the near future if a buyer cannot be found. Ohmeda asked if there was some signal that could come out of this meeting for a development plan that would interest a potential buyer.

In addition, Ohmeda stated that they are struggling to find a pathway that would lead to approval with respect to doing the "right" studies. There is such community contempt for doing placebo controlled, double blinded studies that all possibilities of doing such studies have been exhausted. Dr. Reese Clark's double blind, placebo controlled study has been underway for sometime, but now he is struggling with that study concept so it may peter out. He has kept on schedule by expanding the number of centers (from which babies are referred to him) five times. The number of idiopathic PPHN babies has dwindled and the patient mix has become altered. There are presently 160 patients enrolled out of a 210 patient trial; it will take until the end of this year to complete enrollment. Following the committee meeting, Ohmeda failed to get the investors to see the Reese Clark study to completion. They believe Ohmeda is pursuing a lost cause. If Ohmeda ends up abandoning the studies, they would close down everything including donation of the gas which means that physicians with individual INDs would be getting industrial grade instead of medical grade nitric oxide. Ohmeda acknowledged they may have some obligation to service ventilators that have been purchased from them.

- The Dr. Lipicky stated that the Reese Clark study, provided it shows clinical significance, in addition to the clinical data that Ohmeda already has, would be enough for approval.

- If Dr. Clark is having difficulty enrolling patients because of single center INDs, the Division is prepared to follow the Advisory Committee recommendation by enforcing a more disciplined and controlled policy on those IND holders. Dr. Lipicky asked Ohmeda to provide the names and addresses of those hospitals that are interfering with enrollment in Dr. Clark's study. Dr. Fenichel added that Ohmeda would need to provide the Agency with information as to exactly how those hospitals are interfering with Dr. Clark's enrollment so that the Division can obtain concurrence from other parts of the Agency who will be involved in restricting the INDs.

- Ohmeda stated that the Agency's acceptance of the Reese Clark study, should it be positive, and the Agency's willingness to control the competing INDs is good news. INO Holding Inc. had asked for a close-out plan for INO for next week. Ohmeda will go to them with this information and try to get them to fund nitric oxide until the end of the Reese Clark study.

The Division asked Ohmeda if they would consider pursuing another indication, e.g., use of nitric oxide in heart transplant patients.

- Ohmeda stated that they were not opposed to a new indication, but since they have not been able to get financial backing from anyone to see them through the next 24 months, they believed they were stuck with the PPHN and ARDS indications given the time frame. They believe that if they are to get any backing, it would be on something they had already started.

The Division asked if Ohmeda would be resubmitting the nitric oxide NDA this June.

- Ohmeda stated that if the development plan continues, they plan to resubmit the NDA around February of 1999 after the Reese Clark study has been completed and analyzed.

Ohmeda stated that the ARDS trial is very expensive and there is skepticism as to whether it will be fruitful. They asked it would be acceptable to combined the two ongoing trials into one, and if it were positive, do a second trial.

- The Division did not believe Ohmeda would be able to do a second trial if the combined trial were successful but agreed that Ohmeda could combine the trials if they did so as a last resort.

Action Items:

1. Ohmeda will provide information on how centers involved in the Reese Clark study are interfering with Dr. Clark's enrollment of patients and will include the centers' names, addresses and telephone numbers.

2. The Division will explore the regulations as to how to put those INDs on hold.

Signature minutes preparer: /S/ 5/22/98

Concurrence, Chair: /S/ 6/1/98

Orig. IND
HFD-110
HFD-111/McDonald
HFD-111/Benton
HFD-570/Himmel
HFZ-450/Bazaral

Z. McDonald

JUN 17 1997

RECORD OF TELEPHONE CONVERSATION

Date: June 12, 1997
NDA # 20-845
Product: Nitric Oxide
Sponsor: Ohmeda
Contact: Priya Jambhekar
Phone#: 908-604-7722

Ms. Jambhekar had faxed Dr. Lipicky a copy of Ohmeda's proposed press release regarding the nitric oxide NDA submission for his review. I telephoned Ms. Jambhekar to let her know that Dr. Lipicky requested the following change to the second sentence of the first paragraph:

From:

to:

Inhaled NO's therapeutic potential...

She agreed to make that change.

In addition, in the cover letter (attached) to Dr. Lipicky, Ohmeda made the following statement:

"As discussed during the teleconference, Ohmeda PPD plans to submit the NDA on June 16, 1997 and would like to announce filing of the NDA immediately afterwards".

I pointed out that there is a difference between submitting an application and filing of the application (applications are not filed until 60 days after the date of receipt at the Agency or 60 days from the date payment is received) and asked if Ohmeda really meant to say they, "would like to announce filing... ." Ms Jambhekar said that was a mistake; they meant to say they, "would like to announce the submission of the NDA... ."

/S/

Zelda McDonald, RHPM

cc: Orig. NDA
HFD-110
HFD-111/McDonald

Z-McDonald

AUG 4 1997

Minutes of a Meeting

Meeting Date: July 31, 1997
Requested: Our request - July 28, 1997

NDA: 20-845 nitric oxide

External Participant: Ohmeda Inc.

Type of Meeting: Pre-Advisory Committee Meeting

Meeting Chair: Norman Stockbridge, M.D., Ph.D.
Meeting Recorder: Zelda McDonald
External Participant Lead: Priya Jambhekar

FDA Participants:

Norman Stockbridge, M.D.	Team Leader, HFD-110
Douglas Throckmorton, M.D.	Medical Officer, HFD-110
Zelda McDonald	RHPM, HFD-110

Ohmeda Participants:

Priya Jambhekar	Director, Regulatory Affairs, Ohmeda PPD
Richard Straube, M.D.	Director, Clinical Invest. - Inhaled NO, Ohmeda PPD
Linda Wright, M.D.	Special Assistant to the Director, NICHD

Background:
Ohmeda 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. Ohmeda submitted an NDA for nitric oxide on June 16, 1997. 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 preparing for the Cardiac and Renal Advisory Committee (CRAC) meeting scheduled for October 23, 1997.

Discussion Points:

1. Regulatory Decision Making
   The Division explained that the decision to approve or not approve a new chemical entity is made by Dr. Temple, Director, Office of Drug Evaluation I. Dr. Temple usually does not make a decision that is different from what the Advisory Committee recommends, however, it is not rare for Dr. Temple to make a decision that is contrary to the recommendation of the Division. The Division believes there are a number of problems

with the nitric oxide development program, therefore, it is possible that the Division could recommend that nitric oxide not be approved. It is imperative that Ohmeda understand that the Division's recommendation is not the final one.

2. Non-issues

The Division and Ohmeda should work out any data discrepancies before the Advisory Committee meeting. The Advisory Committee should not be having discussions about ambiguities of what happened in the trials.

3. Division Concerns

- The Division noted that the long-term safety data might be coming in too late to be reviewed before the Committee meeting, since the reviews need to be sent to the Committee members 30 days before the meeting date. The Division urged Ohmeda to submit as soon as possible as much long-term safety data as they could.

  Ohmeda asked if they should submit the data tapes before they submit the written discussion of the long-term safety data and whether the format used in the original submission was acceptable. Ohmeda asked if they could discuss only the results in the amendment and not repeat the discussion of the study design.

  The Division said Ohmeda should submit the data tapes as soon as possible and the format was acceptable. Discussion of results only is acceptable; case report forms should be included.

  Dr. Wright asked if the Division would want to see partial long-term data from the NINOS study, and if so, when would the Division want it.

  The Division said that any data would be good, and it should be submitted as soon as possible.

- It is obvious that nitric oxide improves oxygenation acutely, and the trial that most likely would show whether improved oxygenation led to a clinical benefit was the NINOS trial which had a combined mortality/initiation of ECMO endpoint. The trial results were driven by one of these two components. The Division recommended that Ohmeda address the extent to which oxygenation was a determining factor in whether the patient went on to ECMO. The Division recommended that Ohmeda bring some consultants to the Advisory Committee meeting who can explain what factors are involved in the decision as to whether a patient goes on to ECMO. In the NINOS trial there appears to be a large discrepancy between results analyzed as meeting criteria for ECMO versus how many people actually received it. The Division suggested that Ohmeda address this since one supported a clinical benefit of nitric oxide and the other did not.

- It appears that there is no mortality difference between the treated and placebo groups in the NINOS trial, however, mortality leaned in the wrong direction in the treated groups in the INO-1 and INO-2 trials. Ohmeda should think about how they will respond to that. Was the patient population different in the NINOS study? Were the patients in NINOS more representative of patients who would

receive drug in clinical practice? Were the NINOS patients sicker thereby having access to concomitant therapy? The Division cautioned Ohmeda, however, not to undermine the INO-1 and INO-2 trials because those trials are where the long-term safety data is coming from.

4. Advisory Committee Procedures

- The Division explained that the Advisory Committee usually hears a formal presentation by the Sponsor and/or whomever the Sponsor invites to participate. The presentation is scheduled for one hour. The Committee usually asks questions of the Sponsor during the Sponsor's presentation. The Division provides a set of questions to the Committee that the Division wants the Committee's advice on. These questions are answered at the end of the session. One of the Committee members is appointed "lead reviewer" and is supposed to have read the background packages provided by the Sponsor and the Division. There will be questions that the Committee will have to vote on, e.g., "Is the criteria for ECMO different from measuring acute oxygenation index?" At the end, the Committee will vote on whether nitric oxide should be approved. The FDA reviewers almost never make formal presentation to the Advisory Committee, since they have had their say in the written material provided to the Committee.

- Ohmeda said they spoke with Joan Standaert (Executive Secretary, CRAC) who said there would be four members from the Pulmonary Advisory Committee sitting on the CRAC who would be temporary voting members. They asked if there would be additional consultants who would give their opinion but not vote.

  The Division stated that there will be consultants, but at this point did not know who they would be. The Division advised Ohmeda to call Joan periodically to find out the latest developments regarding the Committee.

- Ohmeda asked if the Division would have any comments on the labeling before the Advisory Committee meeting.

  The Division said that any labeling comments would be in the primary reviewer's review (Ohmeda will receive a copy of any reviews provided to the Committee). If the recommendation from the Division is not approval, there will be no comments on labeling. If an approvable letter is issued, that letter will contain a mark-up of the draft labeling. At that point, Ohmeda will have an opportunity to negotiate labeling. Any phase 4 commitments will be in the approvable letter. It is possible there could be a question for the Advisory Committee regarding phase 4 commitments, but that is not likely.

- The Division will need to see a copy of Ohmeda's package to the Advisory Committee before copies are sent to the Committee members. The Division will need 24 hours to make the decision as to whether it is acceptable to send. Ohmeda should take this into consideration with regard to the Committee receiving the background package in a timely manner.

- Ohmeda asked if the Division would be asking for a new analysis of their data.

  The Division said it is unlikely a new analysis would be requested. The Division's statistical reviewer may do new analyses, however, any that he does will be sent on to Ohmeda.

- Ohmeda asked if there were any pre-clinical issues that would be discussed at the Advisory Committee meeting.

  The Division said that the pharmacology reviewer has been asked to look at tolerance and withdrawal of nitric oxide. The Division suggested that Ohmeda address those briefly at the meeting.

Signature minutes preparer: [signature] 8/4/97

Concurrence, Chair: [signature] 8/4/97

Orig. NDA
HFD-110
HFD-111/McDonald
HFD-111/Benton
Drafted 8/1/97 Finaled 8/4/97
RD:
Stockbridge 8/4/97
Throckmorton 8/1/97

AUG - 7 1997

Meeting Date:	July 22, 1997
Type of Meeting:	45-Day Filing Meeting
NDA#:	20-845 I-NO (nitric oxide)
Type:	1 P
Receipt Date:	June 16, 1997
User Fee Goal Date:	December 16,1997
Meeting Chair:	Raymond Lipicky, M.D.
Meeting Recorder:	Zelda McDonald

Attendees:

Raymond Lipicky, M.D.	Director, Div. of Cardio-Renal Drug Products, HFD-110
Robert Fenichel, M.D., Ph.D.	Deputy Director, HFD-110
Norman Stockbridge, Ph.D.	Team Leader, Medical, HFD-110
Shaw Chen, M.D., Ph.D.	Team Leader, Medical, HFD-110
Douglas Throckmorton, M.D.	Medical Officer, HFD-110
Liza Miriam Pina, M.D.	Medical Officer, Div. Pulmonary Drug Products, HFD-570
Albert DeFelice, Ph.D.	Team Leader, Pharmacology, HFD-110
Narendra Oza, Ph.D.	Pharmacologist, HFD-110
Thomas Papoian, Ph.D.	Pharmacologist, HFD-110
Robert Wolters, Ph.D.	Team Leader, Div. of New Drug Chemistry I, HFD-810
Kooros Mahjoob, Ph.D.	Team Leader, Statistics, HFD-710
Walid Nuri, Ph.D.	Statistician, HFD-710
Alfreda Burnett, Ph.D.	Div. Pharmaceutical Evaluation I, HFD-860
Natalia Morgenstern	Supervisory RHPM, HFD-111
Zelda McDonald	RHPM, HFD-111
Jason Gross	Pre-Approval, Compliance

Background
See attached Filing Summary.

Medical/Statistical
Drs. Throckmorton and Nuri stated that the application is acceptable for filing. They plan to be finished with their joint review mid-to-late September 1997.

Medical Consultant
Dr. Pina expects to be completed with her review by mid-August 1997.

Secondary Medical
Dr. Stockbridge expects to be finished with his review mid-to-late September, 1997.

Chemistry
Dr. Wolters attended this meeting for Drs Advani and Zielinski. The chemistry reviews are done. The establishment has been inspected and found acceptable. Ohmeda has requested new N.O. concentrations of 100 and 800 ppm (the current application provides for 400 ppm).
Dr. Wolters told Ohmeda to submit the request as soon as possible. He expects the review for the new concentration to be completed by September 15,1997.

Pharmacology
Dr. Oza stated that most of the studies that were submitted are quotes from the literature, however, the application is acceptable for filing. He expects to be finished with his review by the end of August 1997.

Biopharmaceutics
Dr. Burnett stated that the biopharmaceutical section is acceptable for filing. She expects to be finished with her review by September 15, 1997.

Environmental assessment
Dr. Wolters stated that Dr. Zielinski has completed the environmental assessment and FONSI.

Division of Scientific Investigation (DSI)
Dr. El-Hage communicated to Ms. McDonald that on July 21, 1997, he requested that the Field inspect two sites: in the next 30 days.

Advisory Committee Meeting
This drug is scheduled to be presented before the Cardio and Renal Drugs Advisory Committee on October 23, 1997

Division Goal Date
November 23, 1997

Filing Status
Everyone agreed the application can be filed.

Signature, minutes preparer /S/ 8/7/97

Concurrence Chair: /S/ 8/12/97

cc:
Orig. NDA
HFD-110
HFD-111/McDonald
HFD-111/Benton
Drafted 7/25/97 Finaled 8/7/97
RD:
Burnett 7/25/97
Chen 7/30/97

45-DAY FILING SUMMARY

NDA 20-845 Nitric Oxide

Related INDs: [ ]

Indication: Hypoxic Respiratory Failure in the Newborn

Therapeutic Classification: 1 P

Date of Application: June 16, 1997
Date of Receipt: June 16,1997
PDUFA Goal Date: December 16, 1997
User Fee Status: Ohmeda paid 1/2 of the user fee on June 11, 1997

Assigned Reviewers

Medical:	Douglas Throckmorton, M.D.
Medical Consultants:	Martin Himmel, M.D. - Deputy Director, Div. of Pulmonary Drug Products, HFD-570
	Liza Miriam Pina, M.D. - Medical Officer, Div. Pulmonary Drug Products, HFD-570
Sec. Medical:	Norman Stockbridge, M.D., Ph.D.
Pharmacology:	Narendra Oza, Ph.D.
Chemist:	J. V. Advani, Ph.D.
Statistician:	Walid Nuri, Ph.D.
Biopharmaceuticist:	Alfred Burnett, Ph.D.
Envi. Assessment:	Florian Zielinski, Ph.D.
DSI:	Antoine El-Hage
Project Manager:	Zelda McDonald

BACKGROUND

GENERAL

On June 13, 1993, Ohmeda PPD was granted Orphan Drug designation for use of nitric oxide in the treatment of hypoxic respiratory failure of the newborn. Ohmeda has "exclusive license right to U.S. patent number 5,485,827 for prevention and treatment of reversible pulmonary vasoconstriction of inhalation of nitric oxide with an oxygen containing gas."

Pre-NDA meetings were held on August 27 and September 27, 1996 to discuss the scope of preclinical and clinical data to be included in the NDA.

The NDA consists of 78 volumes. The pre-NDA submission of the chemistry manufacturing, and controls (CMC) section was submitted to the Agency on February 26, 1997.

Foreign Marketing History - According to Ohmeda, to the best of their knowledge, nitric oxide gas for use in treatment of newborns with respiratory hypoxia has not been marketed in any country.

There is no CANDA.

MEDICAL

This NDA includes two randomized, double-blind, placebo-controlled efficacy and safety studies (NINOS and INOSG - also known as the "Roberts Trial"). These studies were conducted by the National Institute of Child Health and Human Development and the Massachusetts General Hospital, respectively. Letters of authorization providing FDA access to the data from these studies in reviewing the Ohmeda NDA are included in the application. The application also contains a randomized, double-blind, placebo-controlled safety study conducted by Ohmeda (INO-01/INO-02). In addition, the application includes an extensive review of safety and efficacy from the preclinical and clinical published literature.

In a July 2, 1997 meeting between HFD-110 and HFD-570 it was agreed that HFD-570 would consult on the NINOS trial, the Roberts Trial and INO 01/02. HFD-570 would perform a clinical review of all three trials as well as provide input on the primary endpoint in the NINOS trial.

Nitric Oxide is scheduled to be presented before the Cardiac and Renal Drugs Advisory Committee on October 23, 1997.

CHEMISTRY

Dr. Advani completed Chemistry Review #1 on April 16, 1997. A Chemistry information request letter was sent to Ohmeda on April 28, 1997. Ohmeda responded on June 17,1997.

EIR - The inspection has been completed. Dr. Advani said he received a verbal report that it was found acceptable. He has not received the written report.

Methods Validation - Dr. Advani sent the request on July 17, 1997.

Request for Trademark Review - Requested March 5, 1997. In Mr. Boring's reply dated May 22, 1997, the trademark, I-NO. was found unacceptable by the Committee. This fact has been communicated to Ohmeda. Ohmeda said they plan to appeal.

REGULATORY REQUIREMENTS/ORGANIZATION

The application, on its face, appears to be will organized and indexed. Patent information and debarment certification were included. Ohmeda has requested five years exclusivity. The application appears to be suitable for filing.

Zelda McDonald
Project Manager, HFD-110

cc:
Orig. NDA
HFD-110
HFD-110/SBenton
HFD-110/McDonald

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Minutes of a Meeting

OCT 16 1996

Meeting Date: September 27, 1996

IND#s [ ] Inhaled Nitric Oxide (INO)

External Participant: Ohmeda Inc.

Type of Meeting: Pre-NDA

Meeting Chair: Raymond Lipicky, M.D.
Meeting Recorder: Zelda McDonald
External Participant Lead: Christopher Schaber

FDA Participants:

Raymond Lipicky, M.D.	Director, Div. of Cardio-Renal Drug Products, HFD-110
John Jenkins, M.D.	Director, Div. of Pulmonary Drug Products, HFD-570
Robert Fenichel, Ph.D., M.D.	Deputy Director, Medical, HFD-110
Peter Honig, M.D.	Team Leader, HFD-570
Norman Stockbridge, M.D.	Team Leader, HFD-110
Raymond Anthracite, M.D.	Medical Officer, HFD-570
Steven Caras, M.D.	Medical Officer, HFD-110
Isaac Hammond, M.D.	Medical Officer, HFD-110
Khin Maung U, M.D.	Medical Officer, HFD-110
Akinwole Williams, M.D.	Medical Officer, HFD-110
Kooros Mahjoob, Ph.D.	Team Leader, Statistics, HFD-710
Zelda McDonald	RHPM, HFD-111

Ohmeda Participants:

Christopher Schaber	Director, Regulatory Affairs, Ohmeda PPD
Richard Straube, M.D.	Director, Clinical Invest. - Inhaled NO, Ohmeda PPD
Linda Wright, M.D.	Special Assistant to the Director, NICHD

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 <u>not</u> 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?

- Division would like to 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.

Signature minutes preparer: /S/ 10/16/96

Concurrence, Chair: /S/ 10/22/96

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OCT 10 1995

Meeting Minutes
Ohmeda Inc. and FDA
April 17, 1995

IND# [redacted]

Drug: Inhaled Nitric Oxide (INO)

Purpose: To discuss the clinical development plan of inhaled nitric oxide, especially primary and secondary endpoints and consideration of an accelerated approval.

FDA Participants:

Robert Temple, M.D.	Director, Office of Drug Evaluation I, HFD-100
Raymond Lipicky, M.D.	Director, Div. of Cardio-Renal Drug Products, HFD-110
Robert Fenichel, Ph.D., M.D.	Deputy Director & Medical Officer, HFD-110
Abraham Karkowsky, Ph.D., M.D.	Group Leader & Medical Officer, HFD-110
Norman Stockbridge, M.D., Ph.D.	Medical Officer, HFD-110
Mary Ann Gordon, M.D.	Medical Officer, HFD-110
Gerald Bunker, M.D.	Medical Officer, HFD-110
Karen Frank, M.D.	Fellow, HFD-110
John Koerner, Ph.D.	Pharmacologist, HFD-110
Florian Zielinski, Ph.D.	Chemist, HFD-110
Zelda McDonald	CSO, HFD-111
James Hung, Ph.D.	Statistician, Div. of Biometrics, HFD-713
Lu Cui, Ph.D.	Statistician, HFD-713
John Jenkins, M.D.	Group Leader, Div. of Pulmonary Drug Products, HFD-150
Raymond Anthracite, M.D.	Medical Officer, HFD-150

Ohmeda Participants:

K. Cronin	INO clinical Project Leader, Ohmeda PPD
Michael Damask, M.D.	Director, Medical Science
Dennis Davidson, M.D.	Assoc. Prof. of Pediatrics, Albert Einstein School of Med. & Attending neonatologist, Long Island Jewish Med. Center
Lawrence Katz, Ph.D.	Dir. Proj. Mgmt. & Clin. Admin., Ohmeda PPD
Andrew Liu, Ph.D.	Director, Clinical Research and Biometrics
Robert Outwater	Senior Director, Worldwide Reg. Affairs, Ohmeda PPD
Isabelle Peszek	Senior Biostat., Biometrics & Clin. Info, Ohmeda PPD
Christopher Schaber	Assistant Dir. Reg. Affairs, Ohmeda PPD

Background:
Ohmeda has submitted an IND for the use of inhaled nitric oxide in the treatment of persistent pulmonary hypertension in the neonate (PPHN). Ohmeda has also initiated a clinical program for Acute Respiratory Distress Syndrome (ARDS) under IND[redacted] Ohmeda met with this Division on December 12, 1994 to discuss Ohmeda's recommendation that the Agency consider an accelerated approval and change in the primary endpoints from the current endpoints of reduction in morbidity/mortality (PPHN) and number of days off mechanical ventilation (ARDS) to an endpoint of improved oxygenation as the primary basis for approval. At that meeting, Mr. Outwater stated that despite comprehensive initiatives to accelerate patient enrollment, the timely clinical development of INO was in jeopardy due to a number of

circumstances present in each study, including the large patient numbers required to prove the current primary clinical outcome endpoints, competing investigator INDs, necessarily restrictive inclusion criteria and small patient populations. Dr. Temple encouraged Ohmeda to consider reducing their study to three groups (thereby lowering the necessary sample size) and keeping the original endpoint (composite of major sequelae). Dr. Temple said the Agency would explore the possibility of limiting individual investigator INDs in the areas where Ohmeda has their sites as these are not collecting data that are relevant to development of the drug. At Ohmeda's request, Dr. Temple said we would consider sending a letter to all neonatologists stating that parents should be advised to enroll their children in Ohmeda's study.
Ohmeda requested this meeting to discuss their PPHN clinical program initiatives and follow-up on proposals made at the December 12, 1994 meeting.

Meeting:
Mr. Outwater stated that Ohmeda had requested this meeting to discuss their revised protocol for PPHN and listed the discussion items as follows:

1. Replacing the original primary endpoint (composite of major sequelae) with the following two variables:

   - sustained time weighted average oxygenation index, and
   - proportion of rescue required.

   The original endpoint, composite of major sequelae, will be analyzed as a important secondary endpoint.

   The estimated sample size based on these two primary endpoints is 176 (N of 88 for each study).

2. Follow-up on proposed letter from FDA to potential neonatal sites recommending neonatologists to refer patients to Ohmeda's controlled INO trials.

3. Follow-up on FDA proposal to close investigator INDs that may be competing for patients with Ohmeda's controlled trials.

4. Discuss possible Advisory Committee Meeting.

5. CANDA requirements.

When asked by Dr. Temple if the study was still proceeding, Ohmeda said yes. There are 29 sites with 74 patients so far. Ohmeda noted again that the N had been changed from 160 in each of two trials for a total of 320 patients to 88 in each of two trials for a total of 176 patients. Ohmeda said they had broadened the echocardiographic inclusion criteria, allowed short term exposure to high-frequency ventilation (HFV) before entering the study and expanded the gestational age and birth weight inclusion criteria.

Dr. Temple said that we would still consider closing individual investigator INDs that were not doing controlled trials, but we would need a study with meaningful endpoints. Ohmeda said that 10% of their established sites were dramatically affected and the new sites are compromised by existing competing sites. Dr. Lipicky said there is also the potential of working with another

company. It is possible to do a study using more than one delivery system, however, it would involve some potential sharing. Ohmeda said that their position for now is that it does not make sense for them to become involved with another company. They have consulted experts and over the past one and a half years have gained enough knowledge so they know what they need to study. With regard to equipment, Ohmeda believed the data would not be reliable if it were the gathered from many small trials where the equipment was not adequately supervised and NO_2 levels were not measured.

Dr. Davidson introduced himself as the principle consultant for the nitric oxide study. He described the time weighted oxygen index (new primary endpoint) as follows:

$$\frac{OI - FiO_2 \times Paw}{PaO_2}$$

Dr. Fenichel said he understood that what Ohmeda considered therapy failure (before going to nitric oxide) were patients that become hypoxemic, have low mean arterial pressure and are heading toward ECMO. Dr. Temple said that some of the therapy failures were the same as the new primary endpoint. He asked whether other interventions such as HFV would confound the endpoint noting that he thought Ohmeda had amended their application to allow for HFV. Dr. Davidson said the study criteria stated that the investigator can only use conventional ventilation. HFV could be used on a patient (for up to 6 hours) before he/she enters the trial.

Ohmeda presented the major event rates as follows:

	Present Study N=36	Retro N=112
Death	0%	8%
ECMO	14%	36%
Abnormal Neurological Outcome	33%	24%
BPD/RAD	14%	5%

Baseline OI = 28 $\pm$ 10
Rx failures = 50%
Decrease PaO_2, MAP, clin. status = 83% of Rx failures - 42% going to something other than death or ECMO
Median time to Rx failure - 9 hours
Median time to weaning criteria - 33 hours

Dr. Lipicky said the percent total events in the combined endpoints are about as one would expect. Ohmeda agreed, but said a good amount of the abnormal neurological outcomes occur before they get the patients, so it overinflates the numbers. Dr. Lipicky said one could make the argument that abnormal neurological endpoints should not have been included in the combined endpoint. Ohmeda did not agree, stating that the abnormal neurological endpoint should disappear into the tertiary endpoint instead of being a primary endpoint. Dr. Temple asked Ohmeda why they are discouraged with only 36 patients randomized to 4 groups. The results so far may be what one would expect for an effective therapy.

Ohmeda showed another slide with the following major event rates in the first 36 patients:

- PPHN major sequelae lower than expected
- Infants are moderately to severely ill on entry
- Rx failure due to hypoxemia is high and early

Conclusions:

- sustained improvement in 0_2 and secondarily, a decrease in Rx failures would be the appropriate endpoints for the management of PPHN today.
- N (320) based on PPHN major sequelae index has been underestimated and not be attainable.

Dr. Temple said at least one endpoint (ECMO) is folded into the endpoint, so the idea is that 0_2 is better than nothing. He asked what sparked the change in attitude, i.e., using 0_2 as primary endpoint. Ohmeda said they believe they are not going to change the practice of neonatologist using all therapies available. They believe NO should be used as an adjunct to other rescue therapies. Dr. Temple asked why other therapies are needed if the patients get pink. Ohmeda said the patients are extremely labile. Dr. Fenichel said some of the therapies may not be beneficial or, in fact, may be harmful. One is therefore left in the paradoxical situation where the patients that "pinked-up" did better, not because the NO was good, but because they were not exposed to the other harmful therapies.

Dr. Temple said what is being said is that nothing can be done to get the 320 patients as originally planned. He noted that other people are planning to do that though. Ohmeda said they believe the investigators in the NIH study are in for a big surprise regarding death and ECMO. In addition, the patients are not as "clean" since patients receiving surfactant are not excluded. Ohmeda believed use of surfactant confounds the data. Dr. Fenichel said one interpretation would be that an ethical trial cannot be done anymore since Ohmeda is having trouble recruiting.

Ohmeda said it is an economic rather than an ethical problem. Patients are kept at local sites and treated with other therapies. If the local site refers a patient, they lose the income.

Dr. Temple recommended getting everyone together who is doing a controlled trials to talk about the possibility of combining protocols, sharing resources etc. so that something constructive can be accomplished. Ohmeda countered that there are major design deficiencies as well as differences in equipment. Dr. Temple said the studies may start differently, but they could be interpreted together. Dr. Temple encouraged Ohmeda to stay with the original endpoints since the only thing that has happened is recruitment is not good; partly because some of the patients were recruited to the other trials. He said he would like Ohmeda's agreement to attend a meeting with other investigators. Ohmeda said they would consider attending if they could convince Dr. Temple that oxygenation is an acceptable primary endpoint. Dr. Temple said he would not reject the idea, but an Advisory Committee could not be assembled until August/September. He has been hearing persistent skepticism as to whether oxygenation is beneficial, and his experience has been that drugs often do not turn out as predicted. Ohmeda said they would take the message home and let us know soon whether they would be willing to meet.

Dr. Temple summarized the plan as follows:

- We will plan an Advisory Committee to discuss PPHN only for late Summer/early Fall.
- We will try to get some members of the Pulmonary Advisory Committee to sit on the panel.
- Ohmeda will think about attending a meeting with other investigators.

Ohmeda asked if they withdrew their request of using time-weighted oxygenation as a primary endpoint, would we be willing to close down the individual INDs. Dr. Temple said yes, it would be easier to do then. Dr. Lipicky said we would not close them down until after the Advisory Committee meeting where that issue would be discussed openly.

Ohmeda asked Dr. Temple if the Agency was still considering sending letters to all neonatologists recommending that they refer patients to Ohmeda's controlled INO trials. Dr. Temple said we would need to think about how to send such letters. He thought we should talk with Yaffe's group.

/S/

Zelda McDonald, CSO

cc:
HFD-111/McDonald
HFD-111/Benton
HFD-101/Botstein
HFD-150/Hoiberg
HFD-150/Jenkins
HFD-150/Anthracite
HFD-180/Fredd
HFZ-450/Gluck
Drafted 4/27/95 Finaled 10/10/95
RD: Temple
Fenichel 5/2/95
Karkowsky 5/2/95
Stockbridge 5/2/95
Hung 5/5/95
Cui 5/5/95
Anthracite 5/2/95
Jenkins 5/2/95

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OCT 27 1994

Meeting Minutes
Ohmeda Inc. and FDA
~~September~~ October 18, 1994

IND #: [redacted]

Drug: Inhaled Nitric Oxide

Purpose: Pre-NDA (Chemistry)

FDA Participants:

Robert Wolters, Ph.D.	Supervisory Chemist, Div. of Cardio-Renal Drug Prod., HFD-110
Danute Cunningham	Chemist, HFD-110
Zelda McDonald	CSO, HFD-111

Ohmeda Inc:

Jeffrey Jackowski	Associate Director, Regulatory Compliance
Steven Pikulin, Ph.D.	Sr. Assoc. Director, Regulatory Compliance
Steven Heaney	Plant Manager, Airco Specialty Gases

Background:
Ohmeda has submitted an IND for the use of inhaled nitric oxide in the treatment of persistent pulmonary hypertension in the neonate (PPHN). The purpose of this meeting was to discuss the manufacturing and controls requirements for filing a New Drug Application (NDA) for inhaled nitric oxide.

Meeting:

Expected Filing Date
Mr. Jackowski said the earliest filing date would be August or September of 1995.

Nitric Oxide Drug Substance Profile

Synthesis:
Dr. Wolters said the description of the synthesis would need to be more complete. Ohmeda would not need to include the in-process controls, but would need batch records, etc. The mechanism of action should also be included.

A Drug Master File (DMF) would be needed unless the entire synthesis was described in the NDA and [redacted] (or other manufacturing source) is following that exactly. A [redacted] DMF will not be needed.

Manufacturing Site:
General information about the facility needs to be included such as the location, address, general description of the equipment used etc. If the plants are not the same that make the drug substance and the drug product, both will need to be inspected.

Specifications:
Mr. Jackowski said they do not have an assay for measuring nitric oxide, instead they use mass balance. Dr. Wolters said Ohmeda would need an independent assay for nitric oxide such as [redacted] with either an internal or external standard.

Dr. Wolters asked how much [redacted] was present as an impurity. Mr. Jackowski said it was the same as the atmospheric composition. He noted that Ohmeda does have specifications for nitrogen based on the NF but will tighten it up where appropriate.

Stability:
Mr. Jackowski said that they would have one year stability data and 6 months accelerated stability for a Fall 1995 filing date and asked if that would be enough.
Dr. Wolters said if the drug is classified as standard (S), by the time of approval they would have 18 month stability data which would be enough. If the drug is classified as priority (P), there would be a problem. There would be only one year stability on the drug substance, but not the product. Ohmeda asked if they could propose a retest of 6-12 months, and Dr. Wolters agreed.

Dr. Wolters asked Ohmeda in what kind of cylinder the gas was being stored. Mr. Heaney said the stability for the drug substance (concentrated nitric oxide) is being done on gas stored in steel cylinders with stainless steel valves. Dr. Wolters said Ohmeda should state in the NDA their reasons for using steel instead of aluminum cylinders.

Mr. Jackowski said Ohmeda has not decided yet on a concentration for the marketed product and asked if they could bracket the concentration. Dr. Wolters said that 25, 400 and 1600 ppm would be acceptable.

Dr. Wolters noted that Ohmeda would not have to use 75% relative humidity in the stability studies, but they would need to use an accelerated temperature of 40° C. He said that ongoing tests should be carried out at 25° C and at 40° C for 6 months to one year. Ohmeda should also do a stress test at 50° C. Mr. Jackowski asked if Ohmeda needed to do the same for the drug product. Dr. Wolters said Ohmeda should have 1 year stability for the clinical batches.

Nitric Oxide Drug Product Profile

Packaging:
Dr. Wolters asked if the cylinders that are returned are purged.
Mr. Heaney said that they are purged with nitrogen. The cylinders are then put through the same preparation procedure as new cylinders with at least three purges.

Specifications:
Dr. Wolters said Ohmeda should include a test to show that the gas is uniformly mixed in the cylinder, i.e., there is no settling or stratification of gases. The test should be done on older lots of the gas.

Dr. Wolters said Ohmeda would need to justify the impurities in the gas by limits. The history of the specifications should be in the NDA along with adequate data to support those specifications.

Methods:
Dr. Wolters said Ohmeda will need to validate the assay and include a limit of sensitivity (detection). Mr. Jackowski asked if Ohmeda would need identification testing, and Dr. Wolters said yes; IR would be a possibility.

Stability:
Mr. Jackowski asked how the gas would be labeled regarding storage conditions.
Dr. Wolters said Ohmeda would have to comply with the Department of Transportation regulations and asked Ohmeda to let him know what they are. The storage conditions would be based on the stability data.

Mr. Jackowski said the tanks might not be stored in a controlled environment, in fact they may be subject to extreme conditions.
Dr. Wolters said Ohmeda should obtain one year stability data at 40° C.

Environmental Assessment (EA)

Mr. Jackowski asked who would be reviewing the EA.
Dr. Wolters said since the applications is a type 1, Dr. Vincent will be reviewing it. Ohmeda should contact either Dr. Vincent or Christine Good to find out if they will accept an abbreviated EA.

Mr. Heaney said the amount of nitric oxide released into the air from Ohmeda's activities would be minuscule compared to what already gets into the air from the large industrial manufacturing sector.
Dr. Wolters said Ohmeda should predict in the NDA the quantity of the product that gets into the atmosphere over a five year period.
Mr. Heaney said all the gas may not get into the atmosphere because there may be scrubbers.
Dr. Wolters said Ohmeda should present a worst case scenario because he could not predict what Dr. Vincent may require.

Mr. Heaney asked if further testing would involve only the air compartment, and Dr. Wolters said yes, mainly photodegradation testing, but Ohmeda should contact Dr. Vincent with their questions on the EA.

/S/
Zelda McDonald, CSO

cc:
Orig. IND
HFD-111/McDonald
HFD-111/Benton
Drafted 10/25/94 Finaled 10/27/94
RD: Wolters 10/26/94
Cunningham 10/26/94

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Meeting Minutes
Ohmeda Inc. and FDA
March 3, 1994

MAR 22 1994

IND # [ ] Inhaled Nitric Oxide (INO)

Purpose: End-of-Phase II Meeting

FDA Participants:

Robert Temple, M.D.	Director, Office of Drug Evaluation I, HFD-100
Raymond Lipicky, M.D.	Director, Div. of Cardio-Renal Drug Products, HFD-110
Abraham Karkowsky, Ph.D., M.D.	Group Leader & Medical Officer, HFD-110
Norman Stockbridge, M.D., Ph.D.	Medical Officer, HFD-110
Albert DeFelice, Ph.D.	Supervisory Pharmacologist, HFD-110
Narendra Oza, Ph.D.	Pharmacologist, HFD-110
James Hung, Ph.D.	Statistician, Div. of Biometrics, HFD-713
Zelda McDonald	CSO, HFD-111
Kathleen Bongiovanni	CSO, HFD-110

Ohmeda Inc:

Lawrence Alphas	Senior Regulatory Affairs Associate
Michael Damask, M.D.	Director, Medical Science
Lawrence McKay, M.D.	Vice President, Drug Development
Robert Outwater	Senior Director, Worldwide Regulatory Affairs
Isabelle Peszek, Ph.D.	Biostatistician
Andrew Liu, Ph.D.	Director, Clinical Research and Biometrics
Stephen Waters, Ph.D.	Director, Drug Disposition and Product Safety

Background:
Ohmeda has submitted an IND for the use of inhaled nitric oxide in the treatment of persistent pulmonary hypertension in the neonate (PPHN). The intent of this meeting was to focus on the clinical, statistical and toxicology programs that have been discussed with this Division in meetings held on August 26 and November 17, 1993 and January 18 and February 23, 1994. They planned to discuss their final development plans prior to the initiation of the IND program.

Meeting:
Mr. Outwater began the meeting by explaining that Ohmeda considered this meeting to be a mini End-of-Phase II, Pre-Phase III meeting for INO. They wished to discuss the clinical program for PPHN and toxicology requirements (although they have had rather in depth discussions over the last six months with the Division regarding the toxicology of the drug). Mr. Outwater noted that they view the INO project as a combined effort among the gases, devices (scrubber for the NO tank) and the pharmaceuticals Divisions of the company, and they have already had one meeting with the FDA counterparts of those Divisions (Cardio-renal, Devices and Compliance (gas) on August 26,1993).

CLINICAL
Ohmeda plans to carry out two identical, randomized studies in the U.S. of patients with PPHN comparing placebo and 5, 20 and 80 ppm doses of NO.

Dr. Damask presented the major objectives of the clinical studies as follows:

1. To demonstrate the clinical benefits of INO, specifically reduction in morbidity and mortality in PPHN patients.

2. To study the effective and safe dose range for INO in the treatment of acute pulmonary hypertension/hypoxemia.

He noted that there were no good alternatives for the treatment of acute pulmonary hypertension.

Dr. Damask said that Ohmeda's future clinical development plans include Adult Respiratory Distress Syndrome (ARDS) (alterations in pulmonary capillary membrane permeability; pulmonary edema): Sepsis SIRS and Non ARDS acute lung disease (pathology within the alveoli): Pneumonia, aspiration, chest trauma.

Endpoints

Dr. Temple asked if their endpoint would be pulmonary hypertension. Dr. Damask said they planned to focus on harder endpoints such as mortality and morbidity. Dr. Temple said that was excellent but noted that we do not always insist on a mortality effect, e.g., the ability to get off the ventilator significantly sooner could be an important endpoint. Toxicity could influence the choice of an endpoint. Dr. Temple stated that the adult respiratory distress indications would have to be coordinated with the Pulmonary Division.

Dose Response

Dr. Temple asked if Ohmeda had a clear idea of the dose response and how much the oxygenation is improved with respect to PPHN. Dr. McKay said they are not sure what the dose response or correct dose is. The effect is very visible however; the babies turn pink. Doses as low as 1 ppm have been reported effective and reports in the literature show doses up to 80 ppm are effective and tolerated for short periods. NO causes methemoglobinemia in a dose related fashion so that doses above 80 ppm are probably not usable. Dr. McKay also pointed out that nitrogen dioxide (NO_2) which is formed immediately when NO comes in contact with oxygen is quite toxic. Even though a scrubber will remove most pre-formed NO_2, contact of NO with oxygen distal to the scrubber would allow some formation of NO_2. Ohmeda, therefore, is more interested in the lower doses, e.g., 5 - 20 ppm. They consider 80 ppm the upper, maybe even toxic, level.

STATISTICAL ANALYSIS

Dr. Liu said Ohmeda plans to combine the following primary endpoints for analysis:

1. Death on or before the 28th day after birth,
2. Abnormal neurological outcomes (ANO),
3. Requirement for ECMO rescue, and
4. Bronchopulmonary Dysplasia (BPD).

Ohmeda had surveyed eight centers and obtained the following results on the combined efficacy end points:

	Absolute Counts	Mutually Exclusive
Death	8%	8%
ANO	24%	20%
ECMO	36%	28%
BPD	6%	1%
(N=102)		57%

Dr. Liu said the planned 5, 20 and 80 ppm dose groups may not hold their identity (and the previous discussion indicated 5 ppm was expected to be effective) so they plan to combine all dose groups. The reason is that a patient starting with 5 ppm may be moved to 20 ppm and vice versa at least 20% of the time. They also plan to measure blood gases and systemic hemodynamics.

Dr. Liu said the protocol calls for two independent studies in the U.S., 160 patients each. There will be four treatment groups - 5, 20, 80 ppm INO and placebo. The two studies will follow identical protocols. There will be an interim analysis that would allow for possible early stopping.

Dr. Temple commented that the two studies really look like one study. Dr. Lipicky said that in order to be sure they would have an adequate population, they could use the 320 patients and pool them as one study and look at the internal consistency. For a single study to acceptable the p-value would need to be extreme. Dr. Temple noted that in that event the two "substudies" would be likely to show a consistent effect.

Dr. Temple said that it was very important not to stop too soon, especially with an end point that combined mortality and lesser, perhaps more subjective, outcomes. The latter could change on further review. Early stopping should, if possible, be based only on a mortality finding. The consent form should make it clear that the studies will continue until they provide clear evidence of benefit or are complete and will proceed even if results are leaning in a favorable direction.

With regard to the interim analysis, Dr. Temple recommended that a single study, even with a nominal value of .01 significance, would need to have lots of "priors" before it can be accepted. In this case, there is good reason to expect that the better oxygenation resulting from decreased pulmonary pressure and shunt reversal will be beneficial. Nonetheless, Dr. Temple asked Dr. Hung to discuss this issue with the Biostatisticians to see if they are comfortable with the precedent being established. Dr. Lipicky suggested that since ECMO is not done unless the physician thinks the patient will die, ECMO could be a surrogate for death. Dr. Temple agreed. Ohmeda said they would consult FDA before they stopped the study. Dr. Lipicky said we would not advise them on that. Our position is that they should carry out the study as long as they can.

Dr. Temple asked Ohmeda why the interim look would be based on the number of patients instead of the number of endpoints. Dr. McKay said that if NO cured everyone, they would not get enough events (57%) to complete the study, that is why they are looking at the number of patients.

Dr. Temple asked who would be doing the interim analysis. Ohmeda said they planned to do it themselves. Dr. Temple said it is a bad idea for a company to be doing their own interim analysis and recommended that Ohmeda obtain an independent group to look at the deaths and severe adverse events. Ohmeda agreed to do so. In fact, Ohmeda had planned to have an independent group monitoring "safety" but not study outcome. FDA still, in general, did not see how that could be done and urged Ohmeda to use the more usual mechanism of a data monitoring committee that would do the interim look and make the recommendation for discontinuation or further study.

NON-CLINICAL PHARMACOLOGY

Ohmeda had originally planned to do animal studies using ferrets and rats given doses of nitric oxide up to 1000 ppm administered daily by continuous, whole-body inhalation exposure. In a February 23, 1994 meeting (see minutes) with FDA, Ohmeda said they had determined the whole-body system would result in overly toxic concentrations of NO. Ohmeda proposed to do an acute (one-day) study in anesthetized, ventilated dogs and a four week rat, nose-only exposure study; the rat study could expose the animals for six hours per day, however, because of scrubber limitations, Dr. Lipicky concluded that the dog study would be useful but was not sure about the rat. He recommended that these studies be discussed with Dr. Temple at this meeting.

Dr. Lipicky said he thought the acute dog study at the high concentration was worth doing. He did not think the rat study was necessary for the following reasons:

1. We already know that NO is a mutagen and a carcinogen.

2. NO has already been used is humans.

3. The human studies are only two weeks in duration and would be finished long before the long term rat studies.

4. The clinical parameters will pick up the same things that would be picked up in rats, e.g., pulmonary fibrosis.

Dr. Temple asked Dr. Lipicky if he could characterize the extent of the human data that reassures us that a rat study is not needed. Dr. Lipicky said we would look in our files to see what the total exposure is. He thought it would be easy to come up with hundreds of children exposed at Ohmeda's proposed concentrations.

Ohmeda asked if doing the rat study was probably not necessary, and Dr. Temple agreed. Ohmeda asked if they would need rat studies for the other indications (in the adult) they plan to pursue. Dr. Temple said we would have to revisit it.

Dr. DeFelice suggested that perhaps the doses in the dog study could be pushed high enough to cause methemoglobinemia (500 ppm). At that point, administer methylene blue to reverse the methemoglobinemia and cyanosis. The reason for doing this is to make sure the methemoglobinemia and cyanosis is not masking any adverse effects of the NO. That is, when administered up to 500 ppm with the clinical device, is the only acute toxicity a controllable cyanosis?

/S/

Zelda McDonald, CSO

cc:
HFD-111/McDonald
HFD-111/Benton
HFD-101/Botstein
HFD-150/Burke
HFD-180/Fredd
Drafted 3/7/94

RD:	Temple	3/14/94
	Karkowsky	3/8/94
	Stockbridge	3/8/94
	DeFelice	3/9/94
	Oza	3/9/94
	Hung	3/10/94
	Bongiovanni	3/10/94