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Exhibit A

Letter to Robert Outwater, Ohmeda Inc. from N. Morgenstern, Center for Drug Evaluation and Research (August 23, 1994)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 44,124

AUG 23 1994

Ohmeda Inc.
Attention: Mr. Robert I. Outwater
110 Allen Road
P.O. Box 804
Liberty Corner, NJ 07938-0804

AUG 25 1994

Dear Mr. Outwater:

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

We also refer to the End-of-Phase II meeting held on July 25, 1994, between representatives of your firm and this Agency. The following represents our summary of the meeting.

Background:
Ohmeda has submitted an IND for the use of inhaled nitric oxide in the treatment of persistent pulmonary hypertension in the neonate (PPHN). This was an End-of-Phase II meeting to discuss issues relating to Ohmeda's proposed clinical program for Acute Respiratory distress Syndrome (ARDS).

Meeting:
The Clinical Studies
Mr. Outwater said he expected that Dr. Temple would be present at this meeting so that closure could be reached with regard to the issues discussed at the May 16, 1994 meeting. Dr. Lipicky said that Dr. Temple was at the pre-meeting, but could not attend this meeting with Ohmeda; however, he delegated the responsibility of closure to Dr. Lipicky.

Dr. Hyers made a brief presentation of how Ohmeda had come to develop nitric Oxide (NO) followed by an overview of the use of nitric oxide in Europe by Dr. Zapol.

Dr. Lipicky commented that judging from one slide in one patient, the lowest and highest concentrations of NO will affect both oxygenation and pulmonary artery pressure. If there is a clinical benefit, one will not know which was of benefit. He also understood that Ohmeda can not go below 1 ppm and as Dr. Temple said, 80 fold is not bad, however, it would be good if Ohmeda could go lower.

Ohmeda asked if the following were acceptable, and Dr. Lipicky agreed:

- Doses of 1.25 to 80 ppm,
- Two studies with 86 patients each,

- Ohmeda could combine the two studies to get a dose response, and
- The primary endpoint would be the number of days alive off respirator.

Dr. Lipicky noted that if the primary endpoint is not significant, we will not pay much attention to the secondary endpoints.

The Device

Mr. Montgomery presented an overview of the device that Ohmeda is using in their clinical trials. He pointed out that the device is designed to work only with a Siemens ventilator, and the NO and NO2 is monitored 6 inches from the patient on the inspired limb of the Y connector.

Dr. Lipicky asked Ohmeda how they planned to have the device approved.

Ohmeda said they plan to submit a 510K to the Center for Devices and Radiological Health that is not dissimilar to the experimental device except that the commercial device will have the ability to be used on several different kinds of ventilators, not just Siemens. Their goal is to have the device approved at the same time as the drug.

Dr. Gluck said that Ohmeda would have to verify that the device can be used on the different ventilators. Ohmeda agreed noting that they plan to demonstrate the use of the device only with approved, commonly used ventilators.

Ohmeda said that if we thought it would be useful, they would be willing to do a technical seminar on the device. Dr. Gluck said it would be useful, but it should be scheduled more toward the time when Ohmeda is ready to submit the 510K.

Ohmeda asked if the proposed ARDS clinical program (endpoints, sample size) is adequate as the sole basis for approval of inhaled nitric oxide in this application. Dr. Lipicky said yes.

Ohmeda has drafted language for the indications section of the labeling based on the clinical plans for ARDS and PPHN (attached). Assuming positive results, Ohmeda asked if the language was reasonably consistent with what the Agency will approve. Dr. Lipicky said the indications section would be fairly short, not much longer than a sentence. All the statements in the proposed draft would be in the labeling somewhere, but the way Ohmeda has drafted it is not how the indications section would read.

The Toxicology Studies

Ohmeda said they planned to do the acute dog study pushing the dose to see how high they could go and the 7-28 day rat intermittent exposure study and asked if they needed to do any additional work. Dr. Lipicky said no. Dr. Lipicky said he was still concerned about the exposure of health care professionals, noting that

no one seems to know how to study that problem. Ohmeda said they planned to measure the ambient gas around the workers. Dr. Lipicky said they still would not know if, for example, whether the doctors and nurses would eventually get some sort of carcinoma. Ohmeda said they would take measurements to know that they were not exposing the workers beyond a certain limit. That was as much as they could do.

Administrative Concerns

Dr. Stockbridge mentioned that Ohmeda would need to submit a separate IND for the ARDs indication. Ohmeda agreed but asked if they would have to wait 30 days before they could start their studies. Ms. McDonald said that Ohmeda should ask for a waiver of the 30 day waiting period in their cover letter and the waiver will be in the acknowledgement letter.

If you have any questions concerning this IND, please contact:

Ms. Zelda McDonald
Consumer Safety Officer
(301) 594-5300

Sincerely yours,

Natalia A. Morgenstern
Chief, Project Management Staff
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