DEPARTMENT OF HEALTH & HUMAN SERVICES

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February 4, 2002

Donald E. Wilson, M.D., M.A.C.P.
Dean, School of Medicine
University of Maryland, Baltimore
655 West Baltimore Street
Baltimore, Maryland 21201-1559

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1174

Research Project: Prospective, Randomized, Muti-Center Trial of 12 ml/kg vs. 6 ml/kg Tidal Volume Positive Pressure Ventilation for Treatment of Acute Lung Injury and Acute Respiratory Distress Syndrome
Principal Investigator: Henry Silverman , M.D.
RPN Number: 429161-109502

Research Project: Prospective, Randomized, Muti-Center Trial of 12 ml/kg vs. 6 ml/kg Tidal Volume Positive Pressure Ventilation and Ketoconazole vs. Placebo for Treatment of Acute Lung Injury and Acute Respiratory Distress Syndrome
Principal Investigator: Henry Silverman , M.D.
RPN Number: 429161-109502

Research Project: A Phase II/III, Randomized, Double-Blinded, Placebo-Controlled Trial of Lisofylline vs. Placebo in Patients with Acute Lung Injury and Acute Respiratory Distress Syndrome
Principal Investigator: Henry Silverman , M.D.
RPN Number: 1098113

Research Project: Prospective, Randomized, Muti-Center Trial of 12 ml/kg vs. 6 ml/kg

Tidal Volume Positive Pressure Ventilation and Lisofylline vs. Placebo for Treatment of Acute Lung Injury and Acute Respiratory Distress Syndrome

Principal Investigator: Henry Silverman , M.D.

RPN Number: 0298116

Research Publication: Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome (N. Engl J Med 2000;342:1301-8)

HHS Project Number: N01-HR46063

Dear Dr. Wilson:

The Office for Human Research Protections (OHRP) has reviewed the University of Maryland at Baltimore's (UMB's) September 28, 2000 report that was submitted in response to OHRP's August 3, 2000 letter to UMB regarding the allegations of possible noncompliance with the Department of Health and Human Services (HHS) regulations for protection of human subjects (45 CFR Part 46) involving the above referenced research.

Based upon its review, OHRP makes the following determinations regarding the above-referenced research:

(1) HHS regulations at 45 CFR 46.116 stipulate that, except as provided elsewhere under the HHS regulations, no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. HHS regulations at 45 CFR 102(c) define a legally authorized representative as an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

OHRP acknowledges the following regarding the above-referenced research:

(a) 46 of the 47 subjects enrolled in the study protocols at UMB were unable to provide legally effective informed consent, and consent for these subjects instead was obtained and documented from another individual (spouse, adult child, parent, adult sibling, or other relative).

(b) Applicable Maryland law under the Health Care Decisions (HCD) Act of 1993

indicates that the following classes of persons, in the specified order of priority, are authorized to provide informed consent to health care on behalf of a patient who is not competent to consent and who has not appointed a health care agent:

(i) A guardian for the patient, if one has been appointed;

(ii) The patient's spouse;

(iii) The adult child of the patient;

(iv) A parent of the patient;

(v) An adult brother or sister of the patient; or

(vi) A friend or other relative of the patient if the person is a competent individual; and presents an affidavit to the attending physician stating:

(1) That the person is a relative or close friend of the patient; and

(2) Specific facts and circumstances demonstrating that the person has maintained regular contact with the patient sufficient to be familiar with the patient's activities, health, and personal beliefs.

(c) A July 26, 1995 legal opinion from the State of Maryland Office of the Attorney General stated the following regarding the basis for proxy consent for participation in research under the HCD Act:

"The Health Care Decisions Act recognizes three possible decision-makers for an incapacitated patient: the patient herself, through an advanced directive; a health care agent; or a surrogate."

"The term 'health care' is not defined. However, other provisions in the Act make its meaning clear. It is synonymous with a procedure or course of treatment that relates to the disease state of the particular patient."

"This decisional framework, requiring a 'health care' judgement framed in terms of the patient's assumed decision about treatment, works well enough for

therapeutic research. So long as there is an articulable link between the research and a possible improvement in the patient's condition, then a 'health care' decision is possible, and the patient's hypothesized wishes would be the basis of it."

"Likewise, the Act's 'best interest' test is entirely focussed (sic) on the impact of a treatment on the patient. A treatment is in the patient's best interest if 'the benefits to the individual resulting from a treatment outweigh the burdens to the individual resulting from that treatment...' §5-601(e). Under this formulation, participation in a clinical trial might be in the patient's best interest if, to use the language of the American College of Physicians, 'the net additional risk caused by the participation is small, and there is scientific evidence that participation is reasonably likely to offer benefits over standard treatment or no treatment, if none exists.' Even the risk that the patient might wind up in the placebo group of a double-blind, placebo-controlled study might be worth the potential benefit. Asked to consent to the patient's participation in such a research protocol, the proxy would consider the probability and nature of the benefit, the degree of risk, and the opportunity cost of forgone alternatives."

(d) UMB interprets applicable Maryland law under the HCD Act, based on the July 26, 1995 legal opinion of the Maryland Office of the Attorney General, as authorizing a surrogate, as listed in the HCD Act, to consent on behalf of a subject to the subject's participation in the procedures involved in the research.

(2) OHRP finds that the informed consent documents reviewed and approved by the UMB IRB failed to adequately describe the reasonably foreseeable risks and discomforts of the research, in accordance with the requirements of HHS regulations at 45 CFR 46.116(a)(2). In specific, OHRP finds that the informed consent documents failed to describe the following risks and potential discomforts associated with the non-traditional, 6 ml/kg tidal volume group that were described in the UMB IRB-approved protocol: dyspnea, agitation, potential need for higher doses of sedatives and paralytics, volume overload, and hypernatremia.

(3) OHRP finds that the UMB IRB approved informed consent document for research under RPN Number 429161-10952 (ketoconazole vs. placebo) failed to include an explanation of whom to contact for answers to pertinent questions about the research subjects rights and whom to contact in the event of a research-related injury to the subject as required by HHS regulations at 45 CFR 46.116(a)(7).

Corrective Action: OHRP acknowledges that the research has been completed. Furthermore, OHRP acknowledges that UMB has implemented appropriate corrective actions under its MPA to ensure that informed consent documents approved by the IRB include all elements required by HHS regulations at 45 CFR 46.116(a).

(4) HHS regulations at 45 CFR 46.117(a) require that informed consent be documented by use of a *written* consent form approved by the IRB and that is signed by the subject or the subject's legally authorized representative, unless the IRB waives this requirement in accordance with 45 CFR 46.117(c). An IRB may waive the requirement for the investigator to obtain a signed consent in accordance with 45 CFR 46.117(c) if it finds either that (a) the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality, or (b) the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. OHRP notes that the signature page of the UMB IRB-approved informed consent documents for research under RPN Number 429161-10952 provides for witnessed telephone consent of the patient's representative. OHRP notes also that the first sentence of section 10. Human Subjects of the IRB approved protocol under RPN Number 429161-10952 states: "All protocols will require that all study participants or a member of a patient's family sign and date an informed consent." OHRP finds that the UMB IRB-approved informed consent documents permitting witnessed telephone consent by the subject's legally authorized representative fail to comply (i) with the requirements for waiver of documentation of informed consent as required by 45 CFR 46.117(c); and (ii) with the provisions for informed consent described in the protocol.

Required Action: OHRP acknowledges that the research has been completed. By March 8, 2002, UMB must submit to OHRP a detailed corrective action plan to address finding (4) above for any ongoing or planned research activities.

Based upon its review, OHRP has the following additional questions and concerns regarding the above-referenced research:

(5) HHS regulations at 45 CFR 46.116(a)(1) require that when seeking informed consent, each subject be provided with, among other things, a description of the procedures to be followed, and identification of any procedures which are experimental.

OHRP notes the following statement in the above-referenced publication (N. England J Med 2000;342:1301-8):

> "Traditional approaches to mechanical ventilation use tidal volumes of 10 to 15 ml per kilogram of body weight."

OHRP is concerned that the UMB IRB-approved informed consent document failed to describe the 12 ml/kg tidal volume as being the traditional volume used for ventilatory support and the 6 ml/kg as being experimental or non-traditional. Furthermore, OHRP is concerned that the following statements in the UMB IRB-approved informed consent documents were misleading because it implied that both tidal volumes were used with equal frequency in clinical practice at UMB:

> "Presently, doctors use varying volumes of oxygen-enriched air to inflate your lungs. The large and small volumes used by the breathing machine are both standard treatments, but it is unknown whether it is better to use a large or small volume of oxygen-enriched air to inflate the lungs of patients with a lung injury like yours."

> "Presently, doctors use varying volumes of oxygen-enriched air to inflate your lungs. It is unknown whether it is better to use a large or small volume of oxygen-enriched air to inflate the lungs of patients with a lung injury like yours...The large and small volumes used by the breathing machine are both standard treatments."

> "Of the procedures listed above, only the administration of ketoconazole for acute lung injury is experimental. The large and small volumes used by the breathing machine are both standard treatments."

> "Both ways of inflating your lungs are acceptable methods and are commonly used in medical practice."

Please respond. In your response, please clarify (a) the relative frequency with which 12 ml/kg and 6 ml/kg tidal volumes were used in clinical practice at UMB at the time the research was initially reviewed by the UMB IRB; (b) whether the UMB IRB was aware of these statistics when it initially approved the research; and (c) which members of the UMB IRB who participated in the initial and continuing review of the protocol had expertise in critical care medicine and ventilatory support.

(6) HHS regulations at 45 CFR 46.111(b) stipulate that in order to approve research, the IRB shall determine that when some or all of the subjects are likely to be vulnerable to coercion or undue influence, additional safeguards have been included in the study to protect the rights and

welfare of the subjects. OHRP is concerned that (a) both the subjects of the research, because of their impaired mental state, and the subjects' family members, because of the psychological stress of having a critically ill family member being treated in an intensive care unit, appear to have likely been vulnerable to coercion or undue influence; and (b) the UMB IRB failed ensure that there were additional safeguards include in the study to protect the rights and welfare of these vulnerable subjects. In particular, OHRP notes a lack of important details regarding the recruitment and enrollment of subjects, and finds no evidence in the UMB IRB-approved protocol or other relevant UMB IRB records that additional safeguards were included during the subject recruitment and enrollment process. Please respond in detail.

Please submit UMB's response to the above questions and concerns so that OHRP receives it no later than March 8, 2002. If upon further review of the questions and concerns UMB identifies additional instances of noncompliance with the HHS regulations for protection of human subjects, please include detailed corrective action plans to address the noncompliance.

OHRP appreciates the continued commitment of your institution to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Robert J. Meyer
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. Anne N. Hirshfield, Assistant Dean for Research, UMB
Dr. Paul Fishman, Chair, IRB Chair, UMB
Dr. John Mather, Director, Office of Research Compliance and Assurance, Veterans Health Administration
Commissioner, FDA

Dr. David A. Lepay, FDA
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Dr. Greg Koski, OHRP
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Dr. Jeffrey M. Cohen, OHRP
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