DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
Rockville, Maryland 20852

[January 12, 2006]

Philip A. Ludbrook, M.D.
Associate Dean and Chairman, Institutional Review Board
Human Studies Committee Office
Box 8089
Washington University Medical Center
660 South Euclid Avenue
St. Louis, Missouri 63110-1093

Re: Secretary's Determination under Department of Health and Human Services Regulations at 45 CFR 46.407/Commissioner's Determination under Food and Drug Administration Regulations at 21 CFR 50.54 on the Research Protocol Entitled "Precursor Preference in Surfactant Synthesis of Newborns"; (HSC 02-0898; NHLBI F32 HL074601); Principal Investigator Dr. Kimberly Spence

Dear Dr. Ludbrook:

We are writing on behalf of the former Acting Assistant Secretary for Health (ASH), Department of Health and Human Services (HHS) and the former Commissioner, Food and Drug Administration (FDA) regarding the subject research protocol. In January 2005, the Washington University Medical Center Human Studies Committee (WUMC-HSC) forwarded the above-referenced protocol to the Office for Human Research Protections (OHRP) for consideration pursuant to requirements of the HHS regulations at 45 CFR 46.407 (i.e., research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children). The proposed research protocol would be funded by the National Heart, Lung and Blood Institute (NHLBI) grant number F32 HL074601. In March 2005, WUMC-HSC was informed the proposed protocol was also subject to FDA regulations at 21 CFR 50.54.

In accordance with the requirements of 45 CFR 46.407 and 21 CFR 50.54, on May 25, 2005, HHS and FDA published a joint *Federal Register* notice soliciting public review and comment on the proposed study. The comment period was open for a period of 25 days. Documents related to the protocol were made available on the OHRP and FDA websites, including the grant proposal, WUMC-HSC protocol application, parental permission documents, data safety monitoring plan, and WUMC-HSC deliberations on the proposed protocol. At that time, FDA also announced meetings of the Pediatric Ethics Subcommittee (PES) of the FDA's Pediatric Advisory Committee (PAC) and of the PAC itself, on June 28, 2005, and June 29, 2005, respectively, to discuss the referred protocol in accordance with 45 CFR 46.407 and 21 CFR 50.54.

Seven comments were received in response to the *Federal Register* notice, and a single comment was received during the open meeting of the PES meeting on June 28, 2005. After substantial discussion and the opportunity for public comment the PES forwarded to the PAC a recommendation that the protocol be approved providing multiple stipulations were met. The PES also included several recommended modifications to the protocol. On June 29, 2005, the PAC discussed and endorsed all recommendations as provided by the PES without modification.

FDA's Office of Pediatric Therapeutics (OPT) in turn recommended that the FDA Commissioner find that the proposed protocol, with the required modifications, met the requirements of 21 CFR 50.54 and could proceed. On September 6, 2005, Dr. Lester Crawford, the then-Commissioner of FDA, approved the protocol as forwarded by OPT, with all of the required modifications. A copy of the Commissioner's approval is enclosed with this letter.

Following consideration of the research protocol, recommendations by the experts, the approval of the protocol by the Commissioner of the FDA under 21 CFR 50.54 (contingent upon several stipulations), and the comments received from the general public, Dr. Cristina Beato, the then-Acting Assistant Secretary of Health, found that the research may be approved under 45 CFR 46.407, and recommended that HHS support the proposed research protocol, contingent upon specific modifications to the proposed research protocol as outlined below. The proposed research protocol, if so modified, would be in conformance with FDA's regulations at 21 CFR part 50 subpart A; 21 CFR part 50 subpart D, sections 50.54 and 50.55; and HHS regulations at 45 CFR part 46, subpart A; as well as 45 CFR part 46, subpart D, sections 46.407 and 46.408 which require that the research (i) present a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; (ii) be conducted in accordance with sound ethical principles; and (iii) have adequate provisions for soliciting the assent of children and the permission of their parents or guardians. For your reference, the ASH's decision memorandum is enclosed with this correspondence.

The required modifications/stipulations are as follows:

1. The principal investigator should refine the inclusion criteria for the comparison group to a greater degree: the PES believed this would help ensure the homogeneity of the comparison group such that it would provide meaningful comparisons to the data generated from the preterm infants.

- Although the ideal comparison group would be intubated and mechanically ventilated infants who are matched for both gestational and chronological age, the PES nevertheless felt the research would in effect be a descriptive, hypothesis-generating study, and that the inclusion of the comparison group would contribute to the overall knowledge potentially generated by the study.

- The PES also recognized that the principal investigator had listed some exclusion criteria for the comparison group. The PES discussed a number of conditions that may impact on surfactant physiology in full-term infants, such as congenital abnormalities resulting in pulmonary hypoplasia and disorders in pulmonary blood flow associated with such conditions as congenital heart disease.

2. The parental permission process and documents must be modified in the following manner:

- Simplification of the language to an eighth grade reading level, including all legally required language about confidentiality and protected health information.
- Deletion of the reference to there being no likely research related risks.
- Framing of the discussion of alternatives to participating in the study from the perspective of research participants, and *not* from that of the investigators. The PES specifically noted that the consent document should mention that one alternative is not to participate in the research.
- Relocating the discussion of alternatives to a section separate from the discussion of benefits of participation.
- De-emphasizing any immediate connection between the data derived from full-term newborns and the understanding of surfactant physiology in preterm infants.
- Removing the template language about "not needing treatment" found at the beginning of the document; the PES agreed that such language should not be included in a document describing a basic physiology study, as it may inadvertently reinforce a therapeutic misconception.

These stipulations must be incorporated into the research protocol, parental permission documents and process as appropriate, approved by the reviewing Institutional Review Board (IRB), and confirmed by OHRP, prior to HHS funding of the research protocol and the enrollment of human subjects. Once the required stipulations have been incorporated into the protocol and related documents and approved by the IRB, the IRB should then forward the approved protocol and parental permission document to OHRP. Upon confirmation that the required changes have been made, OHRP will send a letter to the IRB, NHLBI, and principal investigator indicating that enrollment may begin.

In addition, OHRP and FDA suggest that the reviewing IRB provide additional consideration to the following issue relative to the parental permission process and documents:

The principal investigator should consider having an independent advocate available during the parental permission process.

- There was considerable discussion about the importance of parents having an approachable and independent person to whom they can direct questions about the research.

- This person would be someone approachable, accessible, and available to discuss the research. A key function of such a person would be to assure that the parents, before signing the parental permission document, understood that this was a basic physiology study that offered no therapeutic benefit for the individual infant.

Please do not hesitate to contact us with any questions. Thank you for your continuing commitment to the protection of human subjects.

Sincerely,

[/s/ B. A. Schwetz]

Bernard A. Schwetz, D.V.M., Ph.D.
Director
Office for Human Research Protections
Office of Public Health and Science

[/s/ D. Murphy, MD]

Dianne Murphy, M.D.
Director
Office of Pediatric Therapeutics
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Enclosures

cc:
Dr. Kimberly Spence, WUMC
Dr. Aaron Hamvas, WUMC
Dr. Lana Skirboll, NIH
Dr. Sandra Colombini-Hatch, NHLBI
Dr. Sara Goldkind, FDA
Dr. Melody Lin, OHRP
Dr. Michael Carome, OHRP
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