[November 10, 2005]

TO: Cristina V. Beato, M.D.
Acting Assistant Secretary for Health

FROM: Director, Office for Human Research Protections

SUBJECT: Recommendation for Approval of HHS Support for Research Involving Children-ACTION

ISSUE

Recommendation by the Office for Human Research Protections (OHRP) that the Department of Health and Human Services (HHS) approve with required modifications the proposed research protocol entitled "Precursor Preference in Surfactant Syntheses of Newborns." As required in HHS regulation 45 CFR 46.407, in making this recommendation, OHRP has reviewed the proposed research, considered the opinions of experts in pertinent disciplines, and reviewed all public comments received. In addition, OHRP has considered the position of the Food and Drug Administration (FDA) as detailed in the memorandum signed by the Commissioner on September 6, 2005 (Tab A). This protocol was referred by the Washington University Medical Center Human Studies Committee (WUMC-HSC).

DISCUSSION

Overview of Study Design and Goals:

The proposed study will be an open-label, non-randomized, parallel study in which viable preterm newborns (gestational age 24 to 28 weeks) and full-term newborns receive simultaneous 24-hour infusions of palmitate and acetate (both precursors of pulmonary surfactant) labeled with the stable, non-radioactive, isotope carbon-13. During and following the 24-hour infusion serial assessments of selective precursor uptake will be measured using gas chromatography and mass spectrometry of pulmonary surfactant collected by tracheal aspiration during routine pulmonary care. In addition, two to five blood samples, totaling a maximum cumulative volume of 2.5 ml (½ teaspoon), will be drawn from either an indwelling catheter placed for clinical indications or in association with a clinically indicated blood sample. In other words, there will be no additional procedures performed on participating subjects of this research protocol other than the 24-hour infusion described above. Subjects of the study would include approximately 10 full-term intubated infants with normal lungs and 15-20 viable preterm intubated neonates with respiratory distress syndrome (RDS). To be eligible for the study, full-term infants must

have normal lung function but require intubation due to non-pulmonary conditions such as a cardiac or central nervous system disorder.

The overall goal of the proposed study is to better understand the potential differences in precursor preferences in surfactant synthesis between preterm infants with immature lungs requiring mechanical ventilation and full-term infants with normal lung function requiring mechanical ventilation for non-pulmonary reasons. The specific aims of the protocol described by the principal investigator are:

1. *To determine the rate of surfactant synthesis using de novo synthesized fatty acids (acetate).*
2. *To determine the rate of surfactant synthesis using preformed fatty acids (palmitate).*
3. *To compare the rates of incorporation in preterm infants versus term infants with normal lungs.*

The principal investigator posits that the use of labeled metabolic precursors of surfactant phospholipids provides a unique and powerful approach to evaluate surfactant metabolism in preterm and full-term infants which could possibly lead to a clinically useful intervention to restore pulmonary function in newborns with respiratory distress syndrome.

Background

All human subjects research studies conducted or supported by HHS that are not otherwise exempt under 45 CFR 46.101(b) and that propose to involve children as subjects require IRB review and approval in accordance with the provisions of HHS regulations at 45 CFR part 46, subpart D as well as basic protections required under subpart A. Pursuant to HHS regulations at 45 CFR 46.407, if an IRB reviewing a protocol to be conducted or supported by HHS does not believe that the proposed research involving children as subjects meets the requirements of HHS regulations at 45 CFR 46.404 (research not involving greater than minimal risk), 46.405 (research involving greater than minimal risk but presenting the prospect of direct benefit to the individual), or 46.406 (research involving a minor increase over minimal risk and no prospect of direct benefit to the individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition), and was suitable for review under the procedure provided in 45 CFR 46.407 (research not otherwise approvable which presents an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of children), the research may proceed only if the following conditions are met:

> (a) The IRB finds and documents that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and

> (b) The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, determine either:
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> (1) that the research in fact satisfies the condition of 45 CFR 46.404, 46.405, or 46.406, or
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> (2) that the following conditions are met:
>
> (i) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
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> (ii) the research will be conducted in accordance with sound ethical principles; and
>
> (iii) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardian, as set forth in 45 CFR 46.408.

Under FDA's Interim Final Rule, effective April 30, 2001 (21 CFR Part 50, subpart D), the FDA adopted similar regulations (21 CFR 50.51, 50.52, 50.53, and 50.54) requiring IRB review to provide additional safeguards for children enrolled in research regulated by the FDA.

After reviewing the protocol, the Washington University Medical Center Human Studies Committee determined that the full study could not be approved under 45 CFR 46.404, 46.405, or 46.406, but that, as required under 45 CFR 46.407, the IRB asserts the study presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children. The Washington University IRB referred the proposed investigation to OHRP on January 13, 2005 for a determination under 45 CFR 46.407. OHRP in turn referred the protocol to the FDA to assess whether the study was subject to FDA regulations. On March 4, 2005, the FDA informed Washington University Human Studies Committee by letter that the proposed study was also subject to 21 CFR part 50, subpart D.

Review of FDA Panel of Experts

On June 28, 2005, the Pediatric Ethics Subcommittee (PES) of the FDA's Pediatric Advisory Committee (PAC) held an open public meeting to discuss the protocol referral from the WUMC-HSC. The PES was comprised of four ethicists, a lawyer, two patient-family representatives, a consumer representative, and pediatric expert consultants in the areas of neonatology, pulmonary medicine, and critical care. There was an opportunity for public comment both prior to the public meeting via the FDA docket, and at the meeting itself in the form of an open public hearing.

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. On June 29, 2005, the PAC met and endorsed all recommendations provided by the PES without modification. The PAC in turn provided the endorsed recommendations to the FDA for consideration. On September 6, 2005, the FDA accepted without modification all

recommendations forwarded by the PAC. The following required stipulations and one recommended modification relevant to the research protocol have been adopted by the FDA and are included in the memorandum signed by the FDA Commissioner on September 6, 2005:

1. Approval Categories

a. The portion of the study involving preterm infants previously diagnosed with RDS could be approved under 21 CFR 50.53 and 45 CFR 46.406 as a clinical investigation involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition. WUMC-HSC had approved the enrollment of the preterm infants with RDS under these regulatory categories, and the PES concurred.

b. The portion of the study involving full-term infants without RDS but who require endotracheal intubation and mechanical ventilation, along with the placement of an intravenous catheter, as part of routine clinical care for non-pulmonary conditions, could be approved under 21 CFR 50.54 and 45 CFR 46.407 as a clinical investigation not otherwise approvable but that presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

c. The risks of the research procedure presented only a minor increase over minimal risk.

   i. The PES noted that the incremental risks of the research beyond the risks of routine clinical care include the rare (less than 2%) risk of infection from the infusion, the possibility of glucose and/or electrolyte disturbances, and the need for a blood transfusion given the additional blood volume taken for research testing.

   ii. During the presentation and discussion, the PES heard data from 53 previously studied infants showing no increase in these adverse events when compared to protocol eligible but not enrolled infants.

   iii. The PES noted that the investigator has gone to great lengths to ensure the safety of the 24-hour infusion

d. The PES concurred with the WUMC-HSC's findings that, although there are no direct benefit to the children included in the research, the proposed clinical investigation presents a "reasonable opportunity" to further the understanding of a serious problem affecting the health or welfare of children since premature births are increasing and have a high morbidity and mortality associated with them (e.g., an average hospitalization of 2-3 months, and potentially significant developmental and medical sequelae).

2. Required Modifications to the Protocol Design

a. 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.

i. 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 exclusion of the comparison group would contribute to the overall knowledge potentially generated by the study.

ii. 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.

3. Required Modifications to the Parental Permission Process and Documents

a. Simplification of the language to an eighth grade reading level, including all legally required language about confidentiality and protected health information.

b. Deletion of the reference to there being no likely research related risks.

c. 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.

d. Relocating the discussion of alternatives to a section separate from the discussion of benefits of participation.

e. De-emphasizing any immediate connection between the data derived from full-term newborns and the understanding of surfactant physiology in preterm infants.

f. 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.

4. **Recommended Modification to the Parental Permission Process and Document (Not Required)**
    a. The principal investigator should consider having an independent advocate available during the parental permission process.
        i. There was considerable discussion about the importance of parents having an approachable and independent person to whom they can direct questions about the research.
        ii. 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.

Public Review and Comment:

On May 25, 2005, a *Federal Register* Notice was published soliciting public review and comment, pursuant to the requirements of 45 CFR 46.407, for a period of 25 days. Documents related to the protocol were made available on the OHRP website, including the proposed protocol, parental permission documents, subject assent documents, and IRB deliberations on the proposed protocol. These documents were also made available on the FDA website, and a docket was established on the FDA website for the submission of public comments.

Seven comments were received in response to the *Federal Register* notice and a single comment was received in the open PES meeting. A verbatim listing of all comments received can be found in Tab B of this letter. In general, four of the comments received in response to the *Federal Register* notice were primarily unsupportive of the study, two were unclear in their position, and one was supportive. The single comment received during the open public period of the Pediatric Ethic Subcommittee meeting was supportive of approving the research. The public comments which were unsupportive of approving this research proposal included a concern about the ethics of conducting research in children in general, a concern about "*bloodstream infection from the 24 hour isotope infusion and the extra blood draws*," a concern about the ethics "*of intubation a perfectly healthy newborn for research*," and a concern about using the proposed "*normal lung*" control group. It appears the last two respondents did not understand that only infants intubated for clinical reason unrelated to the study will be enrolled as controls. More specifically, no infant will be intubated for the purpose of this study. Other concerns and recommendations expressed by respondents included a recommendation for an independent patient advocate to facilitate parental understanding of the research, a request for additional information on the safety experience of the 60 infants that have previously undergone infusions of isotopes at Washington University, a request for clarification on the chemical composition of previous isotope infusions given to infants at Washington University, and a request for clarification on the safety of the infusion relative to possible extravasation and/or accidental co-infusion with incompatible compounds. All comments and concerns were addressed by the PES with recommendations forwarded to and endorsed by the PAC.

OHRP FINDINGS AND RECOMMENDATIONS

OHRP has reviewed the research protocol and other related documents, considered the recommendations provided by the PAC, reviewed the seven comments received from the public, and considered the position of the FDA as outlined in the memorandum from the FDA Commissioner. OHRP concurs with the approval position taken by the FDA and agrees with all required and recommended modifications recommended by the PAC.

In order to approve research under HHS regulations at 45 CFR 46.404 (research not involving greater than minimal risk), the IRB must find that, among other things, the research presents no greater than minimal risk to the subjects. OHRP agrees with the FDA, the PAC, and the WUMC-HSC that the proposed research is not approvable under 45 CFR 46.404 because the research involves the 24 hour infusion of palmitate and acetate which present greater than minimal risk to the subjects.

In order to approve research under HHS regulations at 45 CFR 46.405 (research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects), the IRB must find that, among other things, (a) the risk is justified by the anticipated benefit to the subjects; and (b) the relation of the anticipated benefit to the risk is at least as favorable to the subject as that presented by available alternatives. OHRP agrees with the FDA, the PAC, and the WUMC-HSC that the proposed research is not approvable under 45 CFR 46.405 because the proposed research protocol involves infants who are unlikely to directly benefit from participation in the research.

In order to approve research under HHS regulations at 45 CFR 46.406 (research involving a minor increase over minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition), the IRB must find that among other things, the risk to subjects represent a minor increase over minimal risk and the study is likely to yield generalizable knowledge about the subject's disorder or condition. OHRP agrees with the FDA and PAC that the risk to subjects represents a minor increase over minimal risk for both cohorts (preterm infants with RDS and term-infants with normal lung function) in the study. Similarly, OHRP agrees with the FDA and PAC that the portion of the study involving preterm infants diagnosed with RDS, but not the portion with full-term infants with normal lung function, could be approved under 45 CFR 46.406 since it is likely to yield generalizable knowledge about the subjects' disorder or condition. Since control infants without RDS do not have the condition or disorder under investigation there is no possibility to derive generalizable knowledge about RDS from this cohort, hence 45 CFR 46.406 does not apply.

Contingent upon the WUMC-HSC and the investigator execution of the stipulated revisions to the protocol design and the parental permission process and document outlined below, OHRP finds that the research is approvable under 45 CFR 46.407 because it presents a reasonable opportunity to understand, prevent or alleviate a serious problem (i.e., RDS in preterm infants) affecting the health and welfare of children. OHRP believes that the proposed research

addresses a fundamentally important topic, namely the physiology of surfactant metabolism in preterm infants with RDS. RDS in preterm infants is a relatively common disorder affecting approximately 60-80% of infants less than 28 weeks gestational age. A deficiency in pulmonary surfactant is the primary cause of RDS in preterm infants and is characterized by poor ventilation and severe hypoxia unless the condition is immediately treated with exogenous surfactant. A greater understanding of the metabolism of surfactant in preterm infants with RDS could potentially provide an alternative or adjunctive treatment for this serious condition. Furthermore the investigator asserts no previous human study has investigated the relative contribution of de novo synthesized fatty acids (from acetate) versus preformed fatty acids (palmitate) in surfactant production in newborns.

In determining whether the research would be conducted in accordance with sound ethical principals, OHRP has considered the relevant requirements set forth in 45 CFR 46, subpart A. Under HHS regulations at 45 CFR 46.111(a)(1)(i), the IRB must ensure that risks to subjects are minimized by using procedures which are consistent with sound research design and do not unnecessarily expose subjects to risk; and, HHS regulations at 45 CFR 46.111(a)(2) require the IRB to determine that risks are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of knowledge that may reasonably be expected to result therefrom. HHS regulations at 45 CFR 46.111(a)(3) require an IRB to determine that the selection of research subjects be equitable and that the research setting be particularly cognizant of the special problems of vulnerable research populations, including children. OHRP concludes that the investigator and the WUMC-HSC have taken the appropriate steps to ensure that the study population will be adequately protected.

Regarding whether adequate provisions have been made for soliciting parental permission, in accordance with 45 CFR 46.408, OHRP finds that the protocol, with the stipulated revisions, includes adequate provisions for soliciting parental permission. Solicitation of study subject assent is not applicable to this research due to the age of the subjects.

As stated, OHRP finds that the research protocol can be approved under 45 CFR 46.407, with stipulated revisions to the protocol design and parental permission document and process. OHRP has adopted all of the PAC's recommendations as to required stipulations and recommendations. OHRP refers to the investigator and the reviewing IRB for action on the required revisions and recommendations identified below.

OHRP Required Modifications:

A. Relative to the Protocol

OHRP agrees with all required modifications to the protocol outlined in the FDA memo. See page 4 of this document for a complete listing of required modifications to the protocol design.

B. Relative to the Parental Permission Documents and Process

OHRP agrees with all required modifications to the parental permission process and documents outlined in the FDA memo. See page 4 of this document for a complete listing of required modifications to the parental permission documents and process.

OHRP Recommended Modifications:

Relative to the Parental Permission Process and Documents:

OHRP agrees with the single recommended change to the parental permission process outlined in the FDA memo. See page 5 of this document for a details on the single recommended modification to the parental permission process.

RECOMMENDATIONS

- HHS should support the proposed research protocol entitled "Precursor Preference in Surfactant Synthesis of Newborns," with stipulated revisions to the protocol and parental permission process and documents as outlined above.

- This decision should be made available to the public via appropriate methods, such as placement on the OHRP website.

DECISION

1. HHS should support the proposed research protocol entitled "Precursor Preference in Surfactant Synthesis of Newborns," with stipulated revisions to the protocol and parental permission process and documents as outlined above.

Approved [/s/ Cristina V. Beato, M.D.] Disapproved_____ Date [Nov 18 2005]

2. This decision should be made available to the public via appropriate methods, such as placement on the OHRP website.

Approved [/s/ Cristina V. Beato, M.D.] Disapproved_____ Date [Nov 18 2005]

[/s/ Bernard A. Schwetz]

Bernard A. Schwetz, D.V.M., Ph.D.

2 Attachments:
Tab A - Letter Signed by FDA Commissioner
Tab B - Public Comments on Proposed Protocol