

05-5815



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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MEMORANDUM

**Date:** August 16, 2005

**From:** Sara F. Goldkind, M.D., M.A. *SFG*  
Bioethicist, Office of Pediatric Therapeutics, Office of the Commissioner,  
FDA

**To:** Lester M. Crawford, DVM, Ph.D.  
Commissioner, FDA

**Through:** Murray M. Lumpkin, M.D. *ML*  
Deputy Commissioner for International and special Programs, FDA

Dianne Murphy, M.D. *DM*  
Director, Office of Pediatric Therapeutics, Office of the Commissioner,  
FDA

**Subject:** Pediatric Advisory Committee recommendations regarding  
Commissioner's finding under Food and Drug Administration regulations  
at 21 CFR 50.54 relevant to the research protocol entitled "Precursor  
Preference in Surfactant Synthesis of Newborns," referred jointly to the  
FDA under 21 CFR 50.54 and the Department of Health and Human  
Services under 45 CFR 46.407.

**Pertinent Attachments:**

1. Summary of the Pediatric Ethics Subcommittee of the Pediatric Advisory Committee deliberations, September 10, 2004, drafted by Robert Nelson, M.D., Ph.D., Subcommittee chair
2. Letter from Joan Chesney, M.D., chair of the Pediatric Advisory Committee, July 22, 2005
3. Roster of the Pediatric Ethics Subcommittee members and expert invited guests
4. Roster of the Pediatric Advisory Committee members
5. 21 CFR Part 50 Subpart D *Additional Safeguards for Children in Clinical Investigations* and Federal Register notices regarding protocol referral
6. Summary of public comments received regarding protocol referral

**Issue: Whether the above-referenced proposed clinical investigation involving FDA regulated products is approvable under FDA's human subject protection regulations at 21 CFR Part 50, Subpart D. This protocol was referred by the Washington University Medical Center Human Studies Committee (WUMC-HSC).**

**Overview of Study Design and Goals:**

The principal investigator proposes to administer a 24-hour infusion of stable (non-radioactive) surfactant phospholipid precursors (administered [1,2,3,4-<sup>13</sup>C<sub>4</sub>] palmitate, and [1-<sup>13</sup>C<sub>1</sub>] acetate) and then utilize gas chromatography/mass spectrometry on pulmonary aspirate samples to determine which phospholipid precursor is the preferred substrate for surfactant synthesis. The comparison groups will be viable (as determined by the bedside care team) preterm infants 24-28 weeks gestational age who require mechanical ventilation,<sup>1</sup> and term infants with normal lungs who are mechanically ventilated for non-pulmonary related clinical indications.

According to the protocol, the aims of the study 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 proposed research involves the administration of a 24 hour infusion of palmitate and acetate labeled with the stable (non-radioactive) isotope carbon 13, followed by serial measurements of uptake in pulmonary labeled surfactant obtained by routine, clinically indicated, tracheal aspirate samples. In addition, two to five blood samples totaling a maximum cumulative volume of 2.5 mL 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 as part of this research protocol other than the 24-hour infusion. All infants enrolled in the protocol (including the term infants) will have been intubated for clinical indications. There will be no catheters placed for the research, nor will any additional venipunctures be performed as part of the research.

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 term infants which could possibly lead to clinically useful interventions to restore pulmonary function in newborns with respiratory distress syndrome (RDS).

**BACKGROUND**

The National Heart Lung and Blood Institute (NHLBI) of the National Institutes of Health proposes to fund and conduct a study at the Washington University Medical

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<sup>1</sup> Amendment to the protocol, HSC # 02-0898 "Precursor Preference in Surfactant Synthesis of Newborns," clarifying inclusion criteria with respect to viability, April 18, 2005.

Center (WUMC) entitled, "Precursor Preference in Surfactant Synthesis of Newborns." All studies conducted or supported by the Department of Health and Human Services (HHS) that are not otherwise exempt and that propose to involve children as subjects require Institutional Review Board (IRB) review and approval in accordance with the provisions of HHS regulations at 45 CFR Part 46, Subpart D. Under the FDA's Interim Final Rule, effective April 30, 2001 (21 CFR Part 50, Subpart D), the FDA adopted similar regulations requiring IRB review to provide additional safeguards for children enrolled in clinical investigations regulated by FDA. Since the proposed study would be supported by HHS, and would involve a clinical investigation regulated by the FDA, the study is subject to both HHS and FDA regulations.

After reviewing the protocol, WUMC Human subjects Committee (WUMC-HSC) determined that the study could not be approved under 45 CFR 46.404, 46.405, or 46.406, but that the study presented a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children. Accordingly, pursuant to 45 CFR 46.407, the WUMC-HSC referred the proposed investigation to HHS on 1/13/05. HHS referred the protocol to the FDA for a determination as to whether the study was subject to FDA regulations. On 3/4/05, the FDA informed WUMC-HSC by letter that the proposed study was also subject to 21 CFR Part 50 Subpart D because it is regulated by FDA under section 505(i) of the Federal Food, Drug, and Cosmetic Act.

Pursuant to HHS regulations at 45 CFR 46.407 and FDA regulations at 21 CFR 50.54, if an IRB reviewing a protocol conducted or supported by HHS for a clinical investigation products regulated by the FDA does not believe that the proposed research or clinical investigation involving children as subjects meets the requirements of HHS regulations at 45 CFR 46.404, 46.405, or 46.406, and FDA regulations at 21 CFR 50.51, 50.52, or 50.53, respectively, the research or clinical investigation may proceed only if the following conditions are met:

(a) the IRB finds and documents that the research or clinical investigation 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 Commissioner (FDA) and the Secretary (HHS), respectively, 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:

(1) that the research or the clinical investigation in fact satisfies the conditions of 45 CFR 46.404, 46.405, or 46.406 under HHS regulations, and 21 CFR 50.51, 50.52, or 50.53 under FDA regulations, or

(2) that the following conditions are met:

(i) the research or clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;

(ii) the research or clinical investigation 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 guardians, as set forth in 45 CFR 46.408 and 21 CFR 50.55.

**Summary:** On June 28, 2005, the Pediatric Ethics Subcommittee (PES) of the 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 comments to the FDA docket, and at the meeting itself in the form of an open public hearing.

**The PES, after substantial discussion and the opportunity for public comment, recommended that the protocol be approved, with certain conditions, under 21 CFR 50.54 and 45 CFR 46.407 for the term infants, and under 21 CFR 50.53 and 45 CFR 46.406 for the preterm infants. The PES specific conclusions were as follows:**

**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 intravascular catheters, 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 procedures 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 IRB's findings that, although there is 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 inclusion 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. Deemphasizing 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 Modifications to the Parental Permission Process and Documents (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 he parents, before signing the parental permission document, understood that this was a basic physiology study that offered no therapeutic benefit for the individual infant.

The PES chair presented a summary of the above recommendations to the PAC on June 29, 2005.

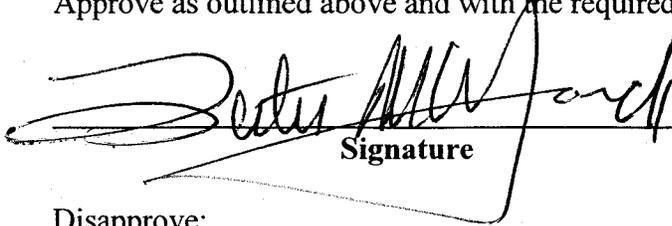
After discussing the recommendations of the PES the PAC endorsed those recommendations with no modifications.

**The Office of Pediatric Therapeutics concurs with the Pediatric Advisory Committee's endorsement of the Pediatric Ethics Subcommittee's recommendations. Therefore, the Office of Pediatric Therapeutics recommends that you find that the proposed protocol, "Precursor Preference in Surfactant Synthesis of Newborns," meets the requirements of 21 CFR 50.54(b) and may proceed as outlined above and with the required modifications.**

**Please indicate by signing at the bottom of this memorandum whether you approve as outlined above, disapprove, or approve with additions/changes the referred proposed clinical investigation. A decision to approve (or approve with additions/changes) signifies that you have made the finding required under 21 CFR 50.54(b). After you make your decision, the Office of Pediatric Therapeutics will transmit a copy of this signed memorandum to the Office for Human Research Protections (OHRP), which will transmit it to the Secretary of HHS via the Assistant Secretary for Health.**

DECISION

Approve as outlined above and with the required modifications:

  
Signature

Date SEP - 6 2005

Disapprove:

\_\_\_\_\_  
Signature Date:

Approve with the following additions or changes:

\_\_\_\_\_  
Signature Date:

Reviewed by:

Donna Katz, JD, OGC, Food and Drug Division

Kevin Prohaska, DO, Medical Officer, Policy Division, OHRP

Irene Stith-Coleman, PhD, Director, Division of Policy and Assurance, OHRP

SUMMARY  
PES RECOMMENDATIONS

## Chair's Summary of the June 28, 2005 Pediatric Ethics Subcommittee meeting

The Pediatric Ethics Subcommittee of the Pediatric Advisory Committee met on June 28, 2005, to review a proposed research protocol entitled "Precursor Preference in Surfactant Synthesis of Newborns." The proposed research would be conducted at the St. Louis Children's Hospital and supported by the National Heart, Lung and Blood Institute. The Washington University Medical Center IRB referred the protocol for review under 45 CFR 46.407 and 21 CFR 50.54 since it determined that the protocol is not approvable under 45 CFR 46.404, 46.405, or 46.406 (21 CFR 50.51, 50.52, or 50.53) yet presents a reasonable opportunity to further the understanding of a serious problem affecting the health of children and could be conducted in accordance with sound ethical principles.

The proposed research involves the administration of a 24 hour infusion of palmitate and acetate labeled with the stable (non-radioactive) isotope carbon 13, followed by the measurement of labeled surfactant obtained by routine clinically indicated tracheal aspiration. In addition, two to five blood samples totaling a maximum cumulative volume of 2.5 mL 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 as part of this research protocol other than the 24-hour infusion. All infants enrolled in the protocol will have been intubated for clinical indications. There will be no catheters placed for the research, nor additional venepunctures performed as part of the research. As such, 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. During the presentation and discussion, the subcommittee heard data from 53 previously studied infants showing no increase in these adverse events when compared to protocol eligible but not enrolled infants. The investigators have gone to great lengths to ensure the safety of the 24-hour infusion. The subcommittee determined (in agreement with the referring IRB) that the risks of the research procedures presented only a minor increase over minimal risk.

The protocol involves two different populations of infants who are intubated for clinical indications. The first population are infants born at a gestational age between 24 and 28 weeks who are studied shortly after birth, at two weeks and four weeks after birth. As of the Continuing Review Report dated September 29 2004, 18 preterm infants have been enrolled in the study. The Washington University Medical Center IRB approved the enrollment of the preterm infants under 45 CFR 46.406. The objective of this portion of the protocol was to study the surfactant production in preterm infants suffering from hyaline membrane disease. As a study of the physiology of surfactant, the research did not offer the prospect of direct benefit to the individual infants enrolled. However, the risk was limited to a minor increase over minimal risk, the research procedures are reasonably commensurate with the experience of preterm infants receiving clinical care for hyaline membrane disease, and the preterm infants have a disorder about which the research may yield generalizable knowledge of vital importance.

The second population are a comparison group of full-term infants who require endotracheal intubation and mechanical ventilation, along with the placement of intravascular catheters, as part of routine clinical care for non-pulmonary conditions. To be included, these infants would need to have a normal chest x-ray and gas exchange as reflected in an inspired oxygen concentration of less than 0.3. The investigators have proposed this population in order to explore the impact of gestational age versus the evolution of chronic lung disease on surfactant kinetics by studying a population of infants without lung disease. Although the ideal comparison group would be intubated and mechanically ventilated infants who are matched for both gestational and

chronological age, such infants would be extremely rare. It is the inclusion of this comparison group that resulted in the referral for federal review under 21 CFR 50.54 and 45 CFR 46.407, for these infants lack the disorder that is the stated objective of study, i.e., surfactant kinetics in preterm infants with hyaline membrane disease. Although the Pediatric Ethics Subcommittee reviewed the amendment in the context of the entire protocol, it is the amendment to include this full-term comparison population that is the focus of discussion.

The subcommittee reviewed the appropriateness of the comparison group drawing on the scientific presentations and expertise of the panel members. Although the protocol as submitted focused on the use of a full-term population as a comparison group to shed light on the data from preterm infants, there are important questions of surfactant physiology and the respective impact of various disease processes and mechanical ventilation that could be usefully examined and would provide important information about this population of full-term infants. Nonetheless, the full-term infants in the comparison group lacked the condition as defined by the submitted protocol (i.e. disordered surfactant physiology as a result of prematurity). The decision to study the intubated full-term infants as a comparison group rather than the primary focus of investigation effectively defined this population as lacking the necessary condition under 45 CFR 46.406 and 21 CFR 50.53. However, the subcommittee believed that a protocol focused on describing surfactant kinetics in an intubated full-term population of infants could have been approvable under 45 CFR 46.406 and 21 CFR 50.53. The subcommittee agreed that referral under 45 CFR 46.407 and 21 CFR 50.54 was appropriate for this protocol *as written*. The subcommittee also agreed that such a referral may not have been necessary if understanding surfactant kinetics in full-term infants who are intubated and mechanically ventilated had been the focus of the investigation.

Following a full discussion of the issues as reflected in the above summary, the subcommittee voted unanimously (11 in favor, no objections or abstentions) in favor of the motion "approvable, with conditions" under the category 21 CFR 50.54 and 45 CFR 46.407. The subcommittee assessed that the proposed research presents a "reasonable opportunity" to further the understanding of a serious problem affecting 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). The subcommittee voted in favor of requiring two conditions for the research to go forward, and of recommending but not requiring a third condition.

The first required condition (11 in favor, no objections or abstentions) focuses on the homogeneity of the comparison group in providing a meaningful comparison to the data generated from preterm infants. The subcommittee 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. The subcommittee recognized that the principal investigator had listed some exclusions in his presentation. As the focus of the proposed research was not on describing the heterogeneity of surfactant physiology in the various conditions affecting full-term infants, careful attention needs to be paid to make sure that this comparison group is relatively homogenous. As mentioned, although the ideal comparison group would be intubated and mechanically ventilated infants who are matched for both gestational and chronological age, the subcommittee felt the proposed research would in effect be a descriptive, hypothesis-generating study, and that inclusion of the comparison group would contribute to the overall knowledge potentially generated by the study. The

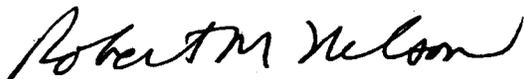
Chair's Summary of the June 28, 2005 Pediatric Ethics Subcommittee meeting

subcommittee recognized that assuring homogeneity may involve a learning process as data about surfactant physiology in intubated full-term infants are obtained.

The second required condition (10 in favor, no objections, one abstention) involves a number of modifications to the parental permission documents reviewed by the subcommittee, particularly the document intended for use in the full-term population. The language needs to be simplified to an eighth grade reading level, including the required language about confidentiality and protected health information. The reference to there being no likely research related risks should be deleted. The discussion of alternatives should be framed from the perspective of research participants, and not from that of the investigators (i.e., the consent document should mention that one alternative is *not* to participate in the research). This discussion should also be highlighted under a section separate from the benefits of participation. The discussion of the purpose of the study should deemphasize any immediate connection between the data derived from full-term newborns and the understanding of surfactant physiology in preterm infants. The template language about not needing treatment found at the beginning of the document should be removed. Such language should not be included in a document describing a basic physiology study, as it may inadvertently reinforce a therapeutic misperception. Finally, there was considerable discussion about the importance of parents having an approachable and independent person to whom they can direct questions about the research. Parents may be intimidated by the inclusion of titles such as "chairman" and "privacy officer" in describing individuals who are available to answer questions about the research.

The third recommended but not required condition (11 in favor, no objections or abstentions) continued the discussion of the importance of parental understanding of the research with the recommendation for an independent advocate to be available during the parental permission process, i.e., someone who would be approachable, accessible, and available to discuss the research. Although the subcommittee came to no conclusion about who such a person should be, there was general agreement about the function of such a person. 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. It should be noted that this recommendation was initially proposed as a mandatory condition, but rejected as such by a majority of the subcommittee (3 in favor, 8 against, no abstentions).

In summary, the Pediatric Ethics Subcommittee of the Pediatric Advisory Committee determined that the proposed research presents a reasonable opportunity to further the understanding of a serious problem affecting the health of children, will be conducted in accordance with sound ethical principles, and that adequate provisions are made for soliciting of the permission of parents or guardians as set forth in 45 CFR 46.408 and 21 CFR 50.55. As such, the Pediatric Ethics Subcommittee recommends that the Pediatric Advisory Committee recommend to the FDA Commissioner and the Secretary of HHS that the research be approved under 45 CFR 46.407 and 21 CFR 50.54 contingent on a satisfactory response to the two required conditions as discussed above.



Robert M. Nelson, M.D., Ph.D.  
Chair, Pediatric Ethics Subcommittee

LETTER  
PAC RECOMMENDATIONS



July 22, 2005

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Lester M. Crawford, DVM, PhD  
Acting Commissioner of Food & Drugs  
Food and Drug Administration

Dear Dr. Crawford:

On June 28, 2005, the Pediatric Advisory Committee (PAC) met to review the Summary Recommendations of the Pediatric Ethics Subcommittee review of the protocol referred by the Washington University Medical Center Institutional Review Board (IRB). The protocol entitled "Precursor Preference in Surfactant Synthesis of Newborns" would be conducted at St. Louis Children's Hospital and potentially funded by an NRSA grant to be submitted by a Neonatology Fellow to the NHLBI.

The protocol was referred for review under 45 CFR 46.407 and 21 CFR 50.54 as the Washington University IRB determined that the protocol was not approvable under 45 CFR 46.404, 46.405, or 46.406 (21 CFR 50.51, 50.52 or 50.53). The IRB did however feel that the research presented a reasonable opportunity to further the understanding of a serious problem affecting the health of children and could be conducted in accordance with sound ethical principles.

The Pediatric Ethics Subcommittee met on 6/28/05 and recommended that the study was approvable as long as certain specific conditions were met under the category 45 CFR 46.407/21 CFR 50.54. After presentation and discussion of the Pediatric Ethics subcommittee's conclusions, the PAC endorsed the Subcommittee's summary as presented with no additional recommendations.

Please let me know if you have additional questions or concerns.

Sincerely,

P. Joan Chesney, M.D.  
Chair, Pediatric Advisory Committee

PJC/njw  
Attachment

Cc: Dianne Murphy, MD, Director, Office of Pediatric Therapeutics  
Sara Goldkind, MD, MA, Bioethicist, Office of Pediatric Therapeutics  
Bernard Schwetz, DVM, PhD, Director, Office for Human Research Protections  
Robert M. Nelson, MD, PhD, Chair, Pediatric Ethics Subcommittee  
Ann Myers, RPh, MPH, Policy Analyst, Office of Pediatrics Therapeutics



ROSTER  
PES

**Pediatric Ethics Subcommittee of the Pediatric Advisory Committee  
Meeting Roster for June 28, 2005**

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**Guest Speaker:**  
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ROSTER  
PAC

**Pediatric Advisory Committee  
Meeting Roster for June 29-30, 2005**

**CHAIR**

**P. Joan Chesney, M.D.**

Expertise: Infectious Diseases  
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21 CFR PART 50 SUBPART D  
FEDERAL REGISTER INFORMATION

*Additional Safeguards for Children in Clinical Investigations*

**Under the regulations, IRBs must review clinical investigations involving children as research subjects and approve only those that satisfy the criteria described in the first three categories listed:**

**21 CFR 50.51/45 CFR 46.404** Clinical investigation not involving greater than minimal risk

**21 CFR 50.52/45 CFR 46.405** Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects

**21 CFR 50.53/45 CFR 46.406** Clinical investigations involving greater than minimal risk and no prospect of direct benefit, but likely to yield generalizable knowledge about the subjects' disorder or condition

**21 CFR 50.54/45 CFR 46.407** Clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. **Approval requires federal agency referral and expert panel review**

**FEDERAL REGISTER INFORMATION**

6/6/05, Briefing Information Posted for 6/28/05 Pediatric Ethics Subcommittee Meeting

5/25/05, Notification of Pediatric Ethics Subcommittee Meeting and Call for Comments  
<http://www.fda.gov/ohrms/dockets/98fr/05-10437.htm>

5/25/05, Notice of Pediatric Advisory Committee Meeting. Pediatric Ethics Subcommittee  
Report presentation and discussion  
<http://www.fda.gov/ohrms/dockets/98fr/05-10436.htm>

SUMMARY  
PUBLIC COMMENTS

# Summary of Public Comments

Robert M. Nelson, M.D., Ph.D.  
Chair, Pediatric Ethics Subcommittee  
Pediatric Advisory Committee, FDA

PES Meeting, June 28, 2005

# Seven Public Comments

● Federal government employee (n = 1)

● Health professional (n = 5)

– Academic IRB Chair (n = 1)

● Citizen (n = 1)

# Categories

- “Not Approve”
  - Misunderstood protocol
  - Understood protocol

● Recommendations

● Questions

# “Not Approve”

## Misunderstood protocol (n = 2)

- causes autism
- ET intubation, central catheters “for research”

## Understood protocol (n = 2)

- “risk” of infection and extra blood draws
- risk “greater than minimal”

# Recommendation (n = 1)

- Presence of “research subject advocate” during informed consent and conduct of research

# Questions (n = 3)

## Safety of the infusions?

- Outcomes, adverse events for previous studies (n=60)? Same solution being infused?
- Risk of contamination? (septic shock)
  - Methods of assuring and testing for sterility?
    - Rapid testing before infusion? Assumed 24 hour shelf life? Training and skill of the personnel?
- Complications of extravasation of isotope infusion?

## Questions (n = 3)

Interference with clinical care?

- Infusion of other “life-saving” solutions?
- Discontinue isotope infusion if vascular access needed for medically necessary product?

Use of incomplete data?

- Ineligible? PK of shorter infusion times?