DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
Rockville, Maryland 20852

[May 16, 2006]

Mary Ellen Sheridan, Ph.D.
Associate Vice President for Research
University Research Administration
The University of Chicago
970 East 58th Street
Chicago, Illinois 60637

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 "Gonadotropin Releasing Hormone (GnRH) Agonist Test in Disorders of Puberty"; (Protocol #13472A, NCRR Award #M01RR00055); Principal Investigator: Dr. Robert Rosenfield

Dear Dr. Sheridan:

We are writing on behalf of the Assistant Secretary for Health (ASH), Department of Health and Human Services (HHS) and the Acting Commissioner, Food and Drug Administration (FDA) regarding the subject research protocol. In June 2005, the University of Chicago Institutional Review Board, Biological Sciences Division (UC-IRB-BSD) forwarded the above-referenced protocol, through your office, 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 Center for Research Resources (NCRR) award number M01RR00055. In July 2005, the University of Chicago was informed that 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 October 7, 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 24 days. Documents related to the protocol were made available on the OHRP and FDA websites, including the grant proposal, UC-IRB-BSD protocol application, parental permission documents, child assent documents, and UC-IRB-BSD 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 November 15, 2005, and November 16, 2005, respectively, to discuss the referred protocol in accordance with 45 CFR 46.407 and 21 CFR 50.54.

Eight comments were received in response to the *Federal Register* notice, and no public comments were received during the open public hearing portion of the PES meeting on November 15, 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 a single recommended modification to the protocol. On November 16, 2005, the PAC discussed and endorsed all recommendations as provided by the PES without modification and in addition added two required stipulations and a single recommended modification.

After receipt of the recommendations forwarded by the PAC, the FDA's Office of Pediatric Therapeutics (OPT) reviewed all deliberations and recommendations and decided to add a single required stipulation. Finally, OPT in turn recommended that the Acting FDA Commissioner find that the proposed protocol, with the required modifications, met the requirements of 21 CFR 50.54 and could proceed. On February 2, 2006, Dr. Andrew von Eschenbach, the Acting 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 Acting Commissioner of FDA under 21 CFR 50.54 (contingent upon several stipulations), the comments received from the general public, and OHRP's findings and recommendations, on April 18, 2006, Dr. John Agwunobi, the Assistant Secretary for Health, found that HHS should support the proposed research protocol with stipulated revisions to the protocol and parental permission/child assent process and documents 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:

A. Relative to the Protocol

1. Results from the diagnostic testing of the sleep study and the leuprolide challenge test must not be disclosed to the normal children or their parents since the clinical significance of these results, particularly abnormal results, would be uncertain and could result in psychological harm to the children (e.g., by conveying the false impression that the child was or might be abnormal).

2. All children participating in the proposed study must be given the opportunity to have their samples collected during the study destroyed when they reach the age of majority.

3. There must be a midpoint assessment of the variability of the data collected from the healthy controls and a reaffirmation of the appropriateness of the sample size and reassessment of the utility of that data against the data obtained from the children with a disorder of puberty already collected.

4. The principal investigator must clarify in the protocol any plans he has relative to the longitudinal follow-up of subjects participating in the proposed study.

B. Relative to the Parental Permission/Child Assent Documents and Process

1. The parental permission and assent documents must state clearly, at the beginning of the documents, that the study is not expected to provide direct medical benefit to the children in the control group, and suggestions of direct medical benefit later in the documents must be removed or revised.

2. Although the study only involves a single dose of leuprolide acetate, the consent process and parental permission/child assent documents must briefly address adverse effects from the long-term use of leuprolide.

3. There must be a robust assent monitoring process designed within the framework of the Clinical Research Center.

4. The principal investigator must clarify in the parental permission and child assent documents any plans he has relative to the longitudinal follow-up of subjects participating in the proposed study.

These stipulations must be incorporated into the research protocol, parental permission/child assent 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/child assent document to OHRP (contact person: Dr. Kevin Prohaska). Upon confirmation that the required changes have been made, OHRP will send a letter to your office, UC-IRB- BSD, NCRR, and the principal investigator confirming that all stipulations have been satisfied for support by the NCRR.

In addition, OHRP and FDA suggest that the reviewing IRB provide additional consideration to the following issues relative to the protocol and parental permission/child assent documents and process:

1. The assent monitoring of a sample of healthy control children should be done to assure that they understand that they could refuse to participate.

2. The principal investigator may want to exclude the siblings of enrolled children with abnormalities from the study, as they may experience undue influence in the assent process.

You may contact Dr. Kevin Prohaska at 240-453-8231 or kprohaska@osophs.dhhs.gov if you have 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]

Diane Murphy, M.D.
Director
Office of Pediatric Therapeutics
Food and Drug Administration

Enclosures

cc:
Dr. Robert Rosenfield, UC
Dr. Jonathan Moss, UC-IRB-BSD
Dr. Lana Skirboll, NIH
Dr. Amy Patterson, NIH, OSP
Dr. David Wilde, NIH, NCRR
Dr. Sara Goldkind, FDA
Dr. Melody Lin, OHRP
Dr. Michael Carome, OHRP
Dr. Irene Stith-Coleman, OHRP