DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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June 19, 2006

Ross McKinney, M.D.
Vice Dean for Research
Duke University School of Medicine
Davison Building, Dean's Suite, room 117A
DUMC Box 3461
Durham, NC 27705

RE: Human Research Subject Protections Under Federalwide Assurance FWA-9025

Research Project: Phase I Safety Trial: A Placebo-Controlled, Phase I Clinical Trial to Evaluate the Safety and Immunogenicity of Recombinant Envelope Proteins of HIV-1 gp160 and gp120 in Children ≥1 Month Old with Asymptomatic HIV Infection
Project Number: ACTG #218
Principal Investigator: Catherine Wilfert, M.D. and Ross McKinney, Jr., M.D.

Research Project: Phase I/II Trial: The Safety and Immunogenicity of Live-Attenuated Varicella Vaccine (Varivax) in HIV-Infected Children
Project Number: ACTG #265
Principal Investigator: Catherine Wilfert, M.D. and Ross McKinney, Jr., M.D.

Dear Dr. McKinney:

The Office for Human Research Protections (OHRP) has reviewed the Duke University School of Medicine's (DUSM) March 29, 2006 response to OHRP's February 17, 2006 letter regarding indications of possible noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46) involving the above-referenced research.

Based upon its review, OHRP makes the following determinations:

HHS regulations at 45 CFR 46.111 state that, in order to approve research covered by the regulations, the institutional review board (IRB) shall determine that certain requirements are satisfied. OHRP finds that when reviewing this research, the DUSM IRB failed to obtain sufficient information to make the following determinations required for approval of research under HHS regulations at 45 CFR 46.111.

(1) 45 CFR 46.111(a)(3): Selection of subjects is equitable. In making this determination, IRBs should be particularly cognizant of the special problems of research involving vulnerable populations. In particular, OHRP finds that DUSM IRB records for the above-referenced research demonstrate a failure of the IRB to obtain sufficient information regarding the selection of wards of the state and foster children as research subjects.

(2) 45 CFR 46.111(a)(4): Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with 45 CFR 46.116. In particular, OHRP finds that DUSM IRB records for the above-referenced research demonstrate a failure of the IRB to obtain sufficient information regarding the process for obtaining permission of parents or guardians for wards of the state or foster children.

(3) 45 CFR 46.111(b): When some or all of the subjects (e.g., children) 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 these subjects. In particular, OHRP finds that DUSM IRB records for the above-referenced research demonstrate a failure of the IRB to obtain sufficient information regarding such safeguards with respect to the enrollment of wards of the state or foster children.

Corrective Actions: OHRP acknowledges the following statements in DUSM's March 29, 2006 response:

> We believe our current system of IRB review, including our record-keeping, has overcome the deficiencies noted in your review of the documents related to these three studies....we have substantially changed our procedures and added depth to the IRB's review of each protocol in compliance with 45 CFR 46.111.

OHRP notes that DUSM attached four documents purported to illustrate the changes referenced in their statement above, including a policy statement on research involving minors who are wards of the state, the IRB policy on research involving children, the IRB policy for the determination of risk for research studies involving pediatric populations and a pediatric risk assessment form.

OHRP notes that the policy entitled "Determination of Risk for Research Studies Involving Children" contains subsection G, entitled "Independent Risk/Benefit Assessment by the Chair of Pediatrics." This subsection states that the investigator must consult with the Chair of Pediatrics of the Duke University School of Medicine, or his/her
designee for an independent assessment of the level of risk and the level of benefit to child that is posed by the research. The Chair or his/her designee is asked to record the outcome of this assessment using the Pediatric Risk

> Assessment Form, which will be included by the investigator in the completed packet of materials that is submitted for IRB review."

OHRP has determined that the above corrective actions adequately address the findings noted above and are appropriate under the DUSM Assurance. As a result, there should be no need for further involvement of OHRP in this matter. Of course, OHRP must be notified should new information be identified which might alter this determination.

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,

Karena Cooper, J.D., M.S.W.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. John M. Falletta, Senior Chairman, Chairperson, IRB #10, DUHS IRB
Dr. Victor Dzau, Chancellor for Health Affairs, Duke Univ. Health System
Dr. R. Sanders Williams, Dean, Duke Univ. School of Medicine
Mr. Mark Gustafson, Asst. Univ. Counsel, Duke Univ.
Dr. Joseph Farmer, Chairperson, IRB #1 and #2, Duke University Health System, Inc.
Dr. John Falletta, Chairperson, IRBs #5 and #6, Duke University Health System, Inc.
Dr. John Harrelson, Chairperson, IRB #3 and #4, Duke University Health System, Inc.
Dr. W. Vance Singletary, Jr., Chairperson, IRB #9, Duke University Health System, Inc.
Dr. George Parkson, Chairperson, IRB #7, Duke University Health System, Inc.
Ms. Jody Power, Executive Director, DUHS IRB
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Sam Shekar, NIH
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