DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852
Telephone: 240-453-8297
FAX: 240-453-6909
E-mail:

cweil@osophs.dhhs.gov

June 26, 2006

Donald E. Wilson, M.D., M.A.C.P.
Vice President of Medical Affairs
Univ. of Maryland Baltimore School of Medicine
655 West Baltimore Street
Baltimore, MD 21201

RE: Human Research Subject Protections Under Federalwide Assurance FWA-7145

Research Project: Phase I Study: A Double-Blind Placebo-Controlled Trial of the Safety and Immunogenicity of a Seven Valent Pneumococcal Conjugate Vaccine in Presumed-HIV-Infected Infants (ACTG #292)
Project Number: IRB #1297046
Principal Investigator: Peter Vink, M.D.

Dear Dr. Wilson:

The Office for Human Research Protections (OHRP) has reviewed the University of Maryland Baltimore School of Medicine's (UMD-Balt) March 30, 2006 letter describing corrective actions taken to address OHRP's determinations set forth in its February 17, 2006 letter to UMD-Balt. OHRP finds that the corrective actions, described below, adequately address OHRP's prior findings and are appropriate under UMD-Balt's FWA.

(1) HHS regulations at 45 CFR 46.404-409 require specific findings by the institutional review board (IRB) for approval of research involving children. OHRP found no evidence that the UMD-Balt IRB considered or made the required findings in its initial review and its July 7, 1995 approval of ACTG #292, including approval of the research under one of the permissible research categories set forth at 45 CFR 46.404-407.

Corrective Action: OHRP acknowledges that as part of the IRB's continuing review of the research on June 26, 1998 and May 28, 1999, the IRB documented that this research posed no greater than minimal risk to children under 45 CFR 46.404.

OHRP further acknowledges UMD-Balt's statements that: (a) all IRB determinations are now documented in meeting minutes and (b) current standard operating procedures require the use of specific checklists describing the permissible categories of research involving

children, to ensure that the IRB discusses and documents its determination and justification for involving children as research subjects.

OHRP notes that the nature and extent of any evidence considered by the IRB in designating this Phase1 drug study involving infants "not greater than minimal risk," is unknown. OHRP further notes that IRBs, in fulfilling their obligation under 45 CFR 46.403 to determine whether research involving children may be approved, must obtain information in sufficient detail to make required findings about possible risks, benefits, and generalizable knowledge likely to result from the research.

With respect to research involving children who are wards, OHRP acknowledges that UMD-Balt has developed a specific checklist - Checklist #11B - which outlines the requirements for approving the involvement of wards in research under 45 CFR 46.409. OHRP notes that Checklist #11B does not reflect that the requirements of 45 CFR 46.409 apply only to research involving children that has been approved under 45 CFR 46.406 or 45 CFR 46.407.

(2) HHS regulations at 45 CFR 46.111 state that in order to approve research covered by the regulations, the IRB shall determine that certain requirements are satisfied. OHRP finds no evidence that the UMD-Balt IRB obtained sufficient information to determine that all the requirements of 45 CFR 46.111 were satisfied before approving ACTG# 292, in which two wards of the state were enrolled. Specifically, OHRP finds no evidence that when the UMD-Balt IRB reviewed ACTG #292 it had sufficient information to make the following required determinations:

(a) 45 CFR 46.111(a)(3): Selection of subjects is equitable.

(b) 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. UMD-Balt produced no documentation regarding the process for obtaining permission of parents or guardians for wards in ACTG #292.

(c) 45 CFR 46.111(b): When some or all of the subjects 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. UMD-Balt produced no documentation that the IRB considered whether additional safeguards to protect wards who could be enrolled in ACTG #292 were appropriate.

Corrective Action: UMB has developed standard operating procedures and reviewer checklists pertaining to the regulatory requirements of 45 CFR 46.111, which mandate that the IRB obtain information in sufficient detail to determine whether these requirements are met. IRB members have been educated regarded requirements for obtaining sufficient information to review research, including special protections for vulnerable populations.

As a result of these determinations, there should be no further need for involvement of OHRP in this matter. OHRP appreciates your continued commitment to the protection of human research subjects. Feel free to contact me if you have any questions.

Sincerely,

Carol J. Weil, J.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. Robert Edelman, Chairperson, U Md. Balt. Sch of Med IRBs #1 - #6
Dr. David Lepay, FDA
Dr. Sam Shekar, NIH
Dr. Anthony Fauci, NIH
Dr. Edmund C. Tramont, NIH
Ms. Donna Marchigiani, NIH
Dr. Robinsue Frohboese, OCR
Dr. Bernard Schwetz, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael Carome, OHRP
Ms. Shirley Hicks, OHRP
Dr. Irene Stith-Coleman, OHRP
Dr. Kristina Borror, OHRP
Ms. Patricia El-Hinnawy, OHRP
Ms. Janet Fant, OHRP