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: 240-453-8132
FAX: 240-453-6909
E-mail:kborror@osophs.dhhs.gov

February 17, 2006

Leonard Dryer
Senior Vice President, Chief Financial Officer
Children's Hospital Association
1056 East 19th Avenue
Denver, CO 80218

John R. Sladek, Ph.D.
Vice Chancellor for Research
University of Colorado at Denver and Health Sciences Center
RC1 North, Room 8129
12800 E. 19th Avenue
Aurora, CO 80010

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1494A and Federalwide Assurance -4730

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: Myron J. Levin, M.D.

Research Project: Phase I Safety Trial: A Study to Test the Safety of Recombinant Interleukin-2 (rIL-2) in HIV-I Infected Children
Project Number: ACTG #299
Co-Principal Investigators: Elizabeth McFarland, M.D.

Dear Mr. Dryer and Dr. Sladek:

The Office for Human Research Protections (OHRP) has reviewed the University of Colorado at Denver and Health Sciences Center (UCDHSC)/Children's Hospital Association (CHA) July 14, 2005 response to OHRP's June 10, 2005 letters 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.

OHRP notes that your reports indicated that ACTG #218, and #345 did not include wards of the state. In addition, your reports indicated that ACTG #265 and #299 included wards of the state

but were determined by the UCDHSC institutional review board (IRB) to fall under HHS regulations at 45 CFR 46.405.

Based upon its review, OHRP makes the following determinations regarding the above-referenced research:

(1) HHS regulations at 45 CFR 46.404-409 require specific findings on the part of the IRB for approval of research involving children. OHRP's review of UCDHSC IRB documents for the above-referenced research revealed no evidence that the UCDHSC IRB considered and made the required findings when initially reviewing this research involving children.

Corrective Actions: OHRP acknowledges that, although UCDHSC IRB did not make the required findings at 45 CFR 46.404-409 for initial review and several subsequent continuing reviews, in 2000 the UCDHSC IRB conducted a "second initial review" and approved the research protocols under 45 CFR 46.405. Since 2000 the UCDHSC IRBs utilize checklists which include all the required findings under HHS regulations at 45 CFR part 46, subpart D.

(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. When initially reviewing this research, the UCDHSC IRB failed to obtain sufficient information to make the following determinations required for approval of research under HHS regulations at 45 CFR 46.111.

(a) 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, such as wards of the state and foster children as research subjects.

(b) 45 CFR 46.111(a)(4): Informed consent will be sought from each prospective subject or the subjects's legally authorized representative, in accordance with 45 CFR 46.116.

(c) 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.

Corrective Actions: OHRP acknowledges that, although UCDHSC IRB did not obtain this information for initial review and several subsequent continuing reviews, in 2000 the UCDHSC IRB conducted a "second initial review" and obtained sufficient information from the investigator to make the required findings under HHS regulations at 45 CFR 46.111(a).

OHRP finds that these corrective actions adequately address the above concern and are appropriate under the UCDHSC FWA. As a result of this determination, 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.

At this time, OHRP would like to provide the following guidance:

> (3) OHRP acknowledges that the UCDHSC IRB found that protocol #265 met the requirements of HHS regulations at 45 CFR 46.405. However, OHRP notes that HHS regulations at 45 CFR 46.405 are only for research that presents the prospect of direct benefit to the individual subjects. Protocol #265 involved a control group of children that did not stand to benefit in any way from the research. OHRP notes that it may have been appropriate to approve the research for the control group under HHS regulations at 45 CFR 46.404.

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,

Kristina C. Borror, Ph.D.
Director, Division of Compliance Oversight

cc: Dr. David Lawellin, HPA, and IRB Co-Chair, Children's Hospital Association
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Lana Skirboll, 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
Ms. Patricia El-Hinnawy, OHRP
Ms. Janet Fant, OHRP