DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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June 19, 2006

Lynda D. Curtis
Sr. Vice President / Executive Director
Bellevue Hospital Center
First Avenue & 27th Street
ME 8
New York, NY 10116

RE: Human Research Subject Protections Under Federalwide Assurance FWA-4966

Research Project: Phase I Trial: Safety and Effectiveness of Four Anti-HIV Drug Combinations in HIV-Infected Children and Teens
Project Number: ACTG #377
Principal Investigator: William Borkowsky, M.D.

Dear Ms. Curtis:

The Office for Human Research Protections (OHRP) has reviewed the Bellevue Hospital Center's (BHC) July 12, 2005 and March 30, 2006 responses to OHRP's June 10, 2005 and February 17, 2006 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.

In our February 17, 2006 letter, OHRP addressed the following issues 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 acknowledges BHC's statement in your June 10, 2005 letter that the research was approved under "Category 46.405, though there was no documentation in the minutes of the IRB meeting of an IRB Subpart D determination." OHRP's review of IRB documents for the above-referenced research revealed no other evidence that the IRB considered and made the required findings when reviewing this research involving children.

Corrective Action: OHRP acknowledges that the New York University School of Medicine (NYUSOM) IRB, which the BHC has designated on its FWA, has revised its written procedures for review of research involving children to require documentation of the findings under HHS regulations at 45 CFR 46.404-409 and include a reviewer checklist for that purpose. The IRB has been educated about the HHS regulations at 45 CFR part 46 subpart D and the use of the reviewer checklist and documentation of the findings. In addition, an internal audit confirmed that the IRB has been making the documenting the required findings since July 2005 and will re-review all research at the time of continuing review to ensure that the required findings have been made and documented.

(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 expressed concern that when reviewing this research, the IRB may have 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. In particular, OHRP was concerned that IRB records appeared to demonstrate a failure of the IRB to obtain sufficient information regarding the selection of 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. In particular, OHRP was concerned that IRB records appeared to 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.

(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. In particular, OHRP was concerned that IRB records appeared to 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 Action: OHRP acknowledges that the NYUSOM IRB has revised its written procedures to include a section entitled "Wards" which includes the HHS regulatory and New York City requirements for research involving wards, including providing the IRB with detailed information about the proposed permission/assent process, the identity and authority of individuals who will provide permission for the ward subjects, obtaining required agreement from the Administration for Children's Services, and requirement for advocates for certain types of research. The IRB also plans to require investigators to take training on human subjects protections and specifically for investigators involved in

studies with children to take and pass a module on research involving children. In addition, the Application for New Protocol Review will elicit information from the investigator regarding risks and prospect of direct benefit, plans to involve wards/foster children, plans to appoint an advocate for wards/foster children, and description of the procedures used for determining who is a legally authorized representative for ward/foster children subjects.

OHRP finds that the corrective actions taken adequately address our concerns and are appropriate under the BHC FWA. As a result of this determination, there should be no need for further involvement of OHRP in this matter.

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: Mr. Ernesto Marrero, Director of Research, Bellevue Hospital Center
Dr. Eric Manheimer, Medical Director, Bellevue Hospital Center
Dr. Thomas J. Blanck, IRB Chairperson, New York U School of Medicine
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Sam Shekar, NIH
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Ms. Janet Fant, OHRP