DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
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July 1, 2002

Benjamin Mojica, M.D., MPH
Deputy Commissioner
New York City Department of Health
225 Broadway, 23rd Floor
New York, NY 10007

RE: Human Research Protections Under Multiple Project Assurance (MPA) M-1541

Dear Dr. Mojica:

The Office for Human Research Protections (OHRP) has reviewed your June 5, 2002 report regarding the above-referenced research conducted at the New York City Department of Health (NYCDOH) that was submitted in response to OHRP's April 17, 2002 letter.

Based on its review of your February 21, 2002 and June 5, 2002 reports, OHRP makes the following determinations:

> (1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.109(e) require that continuing review of research be conducted by the IRB at intervals appropriate to the degree of risk and not less than once per year. The regulations make no provision for any grace period extending the conduct of the research beyond the expiration date of Institutional Review Board (IRB) approval.
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> OHRP finds numerous instances in which the NYCDOH IRB failed to conduct continuing review of research at least once per year. According to the List of Active Protocols table submitted with your February 21, 2002 report, it appears that 67 protocols had not received review in the preceeding year. In addition, as early as 1993 continuing review was not always occurring at least once per year; in one case review did not occur for 3 ½ years (92-007).
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> **Corrective Action:** OHRP acknowledges that NYCDOH has taken numerous corrective actions to address this finding, including reducing the size of the IRB to facilitate achieving quorum, implementing a database to track protocols and IRB actions, and suspending all

research that has not been reviewed at least annually. This corrective action appears to adequately address the above finding and is appropriate under the NYCDOH MPA.
(2) HHS regulations at 45 CFR 46.110(b)(1) limit the use of expedited review procedures to specific research categories published in the Federal Register at 63 FR 60364-60367. Generally, if research did not qualify for expedited review at the time of initial review, it does not qualify for expedited review at the time of continuing review, except in limited circumstances described by expedited review categories (8) and (9) at 63 FR 60364-60367.

OHRP finds that the NYCDOH IRB inappropriately used an expedited review procedure for continuing review of some research.

Corrective Action: OHRP acknowledges NYCDOH's statement that the IRB is aware that research qualifies for expedited review only under certain circumstances, and that the NYCDOH is complying with this requirement. However, OHRP is concerned that the NYCDOH IRB still is not implementing the regulatory provisions for expedited review appropriately.

Required Action: Please provide OHRP with a description of additional corrective actions to address the above finding.

(3) HHS regulations at 45 CFR 46.117(a) require that informed consent be documented by the use of a written consent form approved by the IRB and signed by the subject, or the subject's legally authorized representative, unless the IRB waives this requirement in accordance with HHS regulations at 45 CFR 46.117(c). OHRP finds that there was no evidence in the minutes of NYCDOH IRB meetings that the findings required to waive documentation of informed consent for certain research were being made.

Corrective Action: OHRP acknowledges that the NYCDOH IRB currently is improving the process for taking and documenting minutes of IRB meetings to ensure that they reflect specific findings made by either the IRB or the Chair. This corrective action appears to adequately address the above finding and is appropriate under the NYCDOH MPA.

(4) HHS regulations at 45 CFR 46.103(f) require that an institution with an approved assurance shall certify that each *application* for research has been reviewed and approved by the IRB. OHRP finds that the NYCDOH IRB fails to review grant applications.

Required Action: Please provide a corrective action to address this finding. OHRP acknowledges NYCDOH's concern that reviewing every grant application prior to actual funding presents a number of problems. OHRP notes that many of these problems can be addressed. First of all, NIH will not award a grant in which human subjects are involved for non-exempt research unless the grantee has an OHRP-approved assurance and the grantee provides a certification to NIH that the research has been approved by an appropriate IRB,

consistent with 45 CFR Part 46, within 12 months prior to the budget period start date. Under "just-in-time" procedures, the certification of IRB approval is deferred until just prior to funding. IRB approval is not required prior to NIH peer review of an application. Therefore, following peer review and notification of priority score/percentile, applicant organizations should proceed with IRB review for those applications that have not yet received IRB approval and that appear to be in a fundable range. Regardless of when the IRB review occurs, the IRB should ensure that the research described in the application is consistent with any corresponding protocols reviewed and approved by the IRB.

In addition, IRBs may utilize a primary reviewer system, in which only the primary reviewer need review the grant application.

OHRP has the following additional questions and requests:

(5) Please provide OHRP with copies of the complete protocols and IRB file for the following projects as requested in OHRP's April 17, 2002 letter: protocols # 94-024, 94-035, 96-069, 97-027, 97-083, 98-067.

(6) NYCDOH's June 5, 2002 response to OHRP indicated that for protocol #97-027 several continuing reviews were expedited, ostensibly under expedited review category 8(b). However, the response indicated that the trial was in a follow-up period in which medical examinations and blood draws were being performed. Expedited review category 8(b) is for continuing review of research where no subjects have been enrolled and no additional risks have been identified. Please clarify whether or not subjects had been enrolled. If they had, the research would not seem to qualify for expedited review under category 8(b).

(7) NYCDOH's February 21, 2002 report to OHRP indicated that in one study (#99-006) the principal investigator implemented changes without prior review and approval by the IRB, but notified the Chair in a "progress report." The report stated "IRB staff are currently discussing this issue with the investigator." OHRP acknowledges that this study has been suspended. Please provide OHRP with an update of this event and any additional corrective actions taken.

(8) The minutes of the December 6, 2001 IRB meeting expressed a perception among some IRB members that the IRB did not have sufficient expertise to review vaccine trials, although others noted that the research had been reviewed by other bodies that do have the expertise. "Some members also perceived that it would be wrong for the Board to 'turf' the responsibility for oversight of Phase I studies...and that it may be preferable to obtain consultation from experts in the field of HIV vaccine development." However, later in the minutes of that same meeting there was discussion that since the NIH IRB reviewed the study, "in depth comprehension of the underlying science of vaccine development would not be a necessary pre-condition for our local review...."

In its April 17, 2002 letter to NYCDOH, OHRP expressed concern that the NYCDOH IRB is

not sufficiently qualified through the experience and expertise of its members, and the diversity of its members, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects, and as a result of this lack of expertise would not have been able to determine that the risks to subjects would be minimized by using procedures which are consistent with sound research design, as required by HHS regulations at 45 CFR 46.107 and 46.111(a)(1). When members of the IRB recognized the IRB's lack of expertise, there appeared to have been some perception by other members that this expertise was not necessary.

OHRP acknowledges NYCDOH's statement that they believe the NYCDOH IRB is sufficiently qualified, and that IRB members do not need to be "experts" in a particular area. OHRP is concerned that NYCDOH officials may fail to understand the requirements of HHS regulations at 45 CFR 46.107 that the IRB be sufficiently qualified through the experience and *expertise* of its members. Please respond. OHRP notes that HHS regulations at 45 CFR 46.107(f) stipulate that an IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB.

(9) Please provide OHRP with copies of the minutes of the last NYCDOH IRB meeting.

(10) Please provide OHRP with a copy of the revised NYCDOH IRB policies and procedures.

Please submit to OHRP your response to the above determinations and questions no later than August 12, 2002. If upon further review of the concerns and questions, NYCDOH identifies instances of non-compliance with the HHS regulations for protection of human subjects, please include detailed corrective action plans to address the noncompliance.

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.
Compliance Oversight Coordinator
Division of Human Subject Protections

cc: Dr. Thomas Frieden, NYCDOH

Dr. Lucia Torian, NYCDOH IRB Chair
Mr. Wilfredo Lopez, NYCDOH, OGC
Commissioner, FDA
Dr. David Lepay, FDA
Dr.Greg Koski, OHRP
Dr. Melody Lin, OHRP
Dr. Michael Carome, OHRP
Dr. Jeff Cohen, OHRP
Mr. George Gasparis, OHRP
Ms. Yvonne Higgins, OHRP
Mr. Barry Bowman, OHRP