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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
9200 Corporate Blvd
Rockville, Maryland 20850

WARNING LETTER

VIA FEDERAL EXPRESS

JUL 8 2008

James H. Bowers, Jr., M.D.
Chairman
Brookhaven Memorial Hospital Medical Center
Institutional Review Board
101 Hospital Road
Patchogue, NY 11772

Dear Dr. Bowers:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection of your Institutional Review Board (IRB) from March 6 through March 13, 2008 by an investigator from the FDA New York District Office. The purpose of this inspection was to determine whether your IRB is in compliance with applicable federal regulations. IRBs that review investigations of devices must comply with applicable provisions of Title 21, Code of Federal Regulations (21 CFR) Part 56-Institutional Review Boards and Part 50-Protection of Human Subjects. This letter also acknowledges your May 14, 2008 letter that addresses the corrective action you intend to take and the June 12, 2008 letter which contains your written agreement with [redacted] and your IRB.

The inspection was conducted under a program designed to ensure that data and information contained in requests for Investigational Device Exemptions (IDE), Premarket Approval (PMA) applications, and Premarket Notification submissions (510(k)) are scientifically valid and accurate. Another objective of the program is to ensure that human subjects are protected from undue hazard or risk during the course of scientific investigations.

Our review of the inspection report prepared by the district office revealed serious violations of Title 21, Code of Federal Regulations (21 CFR) Part 56 -- Institutional Review Boards, and Section 520(g) (21 U.S.C. 360j(g)) of the Act. At the close of the inspection, the FDA investigator presented an inspectional observations form FDA 483 for your review and discussed the observations listed on the form with you and Mr. Peter Cerone, Director of Pharmacy Services. The deviations noted on the FDA 483 and our subsequent review of the inspection report is discussed below:

Failure to have adequate written procedures governing the functions and operations of the IRB [21 CFR 56.108 (a), (b), and (c)].

Pursuant to FDA regulations, an IRB must prepare, maintain, and follow written procedures that describe the IRB's functions and operations, including: conducting continuing review of research; for determining which projects require review more often than annually, and which project needs verification from sources other than the investigator that no material changes have occurred since previous IRB review; ensuring that changes to approved research may not be initiated without IRB review and approval, except where necessary to eliminate apparent hazards to human subjects; ensuring prompt reporting to the IRB, appropriate institution officials, and the FDA of unanticipated problems involving risks to human subjects; and for ensuring that the review of proposed research are convened at meetings at which the majority of members are present. The IRB's written procedures lacked procedures for the following requirements:

- Continuing review of research and for reporting its findings and actions to the institution and the investigator;

- Determining which projects require review more often than annually and for projects that need verification from sources other than the investigator that no material changes have occurred since the previous IRB review;

- Ensuring prompt reporting to the IRB of changes in research activities; and for ensuring prompt reporting to the IRB, institutional officials, and the FDA of unanticipated problems involving risk to human subjects, of instances of noncompliance with the regulations, and of suspension or termination of IRB approval; and

- Ensuring that the reviewing of proposed research is convened at meetings at which the majority of members are present, including at least one member whose concerns are in nonscientific areas.

Failure to ensure that the IRB reviews proposed research at convened meetings at which a majority of the members are present, including one member whose primary concerns are in nonscientific areas and that no IRB member participates in the initial or continuing review of any project in which the member has a conflicting interest [21 CFR 56.108(c) and 21 CFR 56.107(e)].

Pursuant to 21 CFR 108(c), a majority of members, including at least one member whose primary concerns are in the nonscientific area, is needed to review proposed research at convened meetings. In addition, no IRB may have a member participate in the IRB's initial or continuing review of any project, in which the member has a conflicting interest, except to provide information requested by the IRB as per 21 CFR 56.107(e). You failed to adhere to the above stated regulations. Examples of your failure include, but are not limited to the following:

- At the January 24, 2003 and June 2, 2005 IRB meetings, Dr. R. Rubenstein participated in the review and approval of several studies, for which he was the principal investigator. Our documentation reflects that Dr. R. Rubenstein is the clinical investigator for the [redacted] and [redacted] studies. The IRB's meeting minutes reflect that Dr. Rubenstein was present at both meetings; however, there is no documentation that Dr. Rubenstein refrained from voting on the aforementioned studies during the January 24, 2003 and June 2, 2005 meetings.

Failure to conduct continuing review of research at least annually [21 CFR 56.109(f)].

In accordance with 21 CFR 56.109(f), an IRB shall conduct continuing review of FDA regulated research at intervals appropriate to the degree of risk, but not less than once per year. Examples of your failure to conduct continuing review at least annually include, but are not limited to the following:

- The [redacted] study received initial approval on January 24, 2003. However, continuing review was not performed until July 8, 2004. There has been no documentation of continuing review for years 2005, 2006, and 2007. Also, there is no documentation that the study was suspended during that time.

- The [redacted] study received initial approval on May 28, 2003. However, continuing review was not performed until July 8, 2004.

Failure to maintain adequate documentation of IRB activities, including copies of all meeting minutes, approved consent forms, and progress reports of all research proposals reviewed [21 CFR 56.115(a)(1) and 56.115(a)(2)].

Pursuant to 21 CFR 56.115(a)(1) an IRB shall maintain copies of all research proposals reviewed, scientific evaluations that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects. In addition, pursuant to 21 CFR 56.115(a)(2), the IRB shall prepare and maintain adequate documentation of IRB activities including minutes of IRB meetings which shall be in sufficient detail to show attendance, actions taken, and the vote of these actions including the number of members voting for, against, and abstaining. Examples of your failure to adhere to the above stated regulation include, but are not limited to the following:

- The meeting minutes dated January 24, 2003, July 8, 2004, June 2, 2005, and June 1, 2006, do not reflect the number of members who voted for, the number that voted against, or the number that abstained from voting.

- The IRB approved the [redacted] study at the January 24, 2003. However, records were not maintained and did not include copies of the protocol and the approved informed consent document.

- The [redacted] study was approved on May 28, 2003. However, records of the IRB meeting minutes documenting the discussion and approval of the study were not maintained.

Failure to prepare and maintain a list of IRB members identified by name, earned degree, representative capacity, and the relationship between each member and the institution [21 CFR 56.115(a)(5)].

Pursuant to 21 CFR 56.115(a)(5) an IRB shall prepare and maintain a list of IRB members identified by name, earned degrees, representative capacity, employment or other relationship between each member and the institution. The IRB lists failed to properly identify the IRB membership. Examples of this failure include but are not limited to the following:

- The IRB membership roster has not been updated to include the current IRB Chairperson, James H. Bowers, Jr., M.D., who assumed the role of Chairperson in the fall of 2007. The roster was last updated in 2006.

- The IRB membership rosters do not identify members by their earned degrees, representative capacity, and affiliation with the institution. Therefore, we cannot determine if the IRB adequately met the requirements to review FDA regulated research. For example, an IRB is required to have a nonscientific member present at all convened meetings; however, the IRB rosters and meeting minutes do not reveal which members are nonscientific members.

Your May 14, 2008 letter states that your IRB intends to enter into a written agreement with [redacted] an independent institutional review board located at [redacted] for initial and continuing review of any research done at the Medical Center. You also state that the IRB intends to immediately terminate the internal IRB, once the agreement has been reached. Your written response is inadequate in that you did not provide an explanation how you ensured the protection of human subjects during the transfer of all study records from your IRB to [redacted] Also, you must provide an explanation of how you ensured that the continuing review process was adequately performed for the FDA studies that currently lacked continuing review before transfer of the studies to [redacted] On June 12, 2008, Walter G. Metz, General Counsel, [redacted] provided FDA a copy of the signed written agreement between [redacted] and the IRB with the effective date of June 10, 2008.

The violations described above are not intended to be an all inclusive list of problems that may exist at the IRB. The IRB is responsible for ensuring compliance with the Act and applicable regulations.

Please note during the review of the records, we noted that the IRB failed to conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year. Your written policy should explain how the IRB will make this determination.

Within fifteen (15) working days of receiving this letter, please provide written documentation of the actions you have taken or will take to correct these violations and prevent the recurrence of similar violations. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you. Send your response to: Attention: Linda D. Godfrey, Chief, Program Enforcement Branch, Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, 9200 Corporate Boulevard, HFZ-310, Rockville, Maryland 20850.

A copy of this letter has been sent to New York District Office, 158-15 Liberty Avenue, Jamaica, New York 11433. Please send a copy of your response to that office.

If you have any questions, please contact Linda D. Godfrey, by telephone at 240-276-0125, or by e-mail at Linda.Godfrey@fda.hhs.gov.

Sincerely yours,

Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and
Radiological Health