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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Blvd
Rockville MD 20850

MAR 14 2007

WARNING LETTER

VIA FEDERAL EXPRESS

Bhadresh Patel, MD/Chairperson
Freeport Health Network IRB
1045 W. Stephen Street
Freeport, IL 61032

Dear Dr. Patel:

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 November 15 through November 29, 2006, by an investigator from the FDA Chicago 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, Part 50-Protection of Human Subjects, and Part 812-Investigational Device Exemptions. This letter also requests prompt corrective action to address the violations cited.

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 several 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. The deviations noted on the FDA 483 and our subsequent review of the inspection report are discussed below:

1. **Failure to prepare and follow written procedures for conducting initial and continuing review of research [21 CFR 56.108(a)].**

   This is a repeat of a violation cited in the last IRB inspection in May 2004.

   Review of study documents indicates that the IRB failed to follow or failed to maintain written procedures for conducting initial and continuing review of research. For example:

   a.) The IRB failed to follow its written procedures for informed consent documents. Specifically, the IRB's procedures require that consents for medical research projects will contain specific required elements and additional elements. However the consent form document approved for Study Protocol [redacted] by the IRB on March 18, 2005, was missing the following elements that are required by your procedures:

      i. A description of any reasonably foreseeable risks or discomforts to the subject;

      ii. An explanation of whom to contact for answers to pertinent questions about the research and research subject's rights, and who to contact in the event of a research related injury to the subject.

   b.) The IRB's procedures require that IRB meetings conducted by telephone are done in such a way that each participating member can actively and equally participate in the discussion, and that the minutes of such meetings clearly document that this condition has been met. The IRB failed to adhere to this procedure by conducting "voice votes" for approval of informed consent documents. These votes were conducted by means of an individual phone call to each IRB member by the IRB's Executive Assistant, with a request for their vote. For example:

      i. The initial approval of the consent form for Study Protocol [redacted] was approved by seven IRB members during a "special voice vote meeting" on March 18, 2005. There was no indication in the IRB records that any group discussion of the consent form occurred.

      ii. The approval of the revised consent form for Study [redacted] was approved by nine IRB members during a "special voice vote meeting" on February 24, 2005. There was no indication in the IRB records that any group discussion of the consent form occurred.

   c.) The IRB's Policy did not adequately meet the requirements of 21 CFR 56.108 in

that there were no written procedures for the following:

i. A requirement for ensuring prompt reporting to the Food and Drug Administration of: any unanticipated problems involving risks to human subjects or others; any instance of serious or continuing noncompliance with regulations or the requirements or determinations of the IRB; or any suspension or termination of IRB approval.

ii. A procedure for reporting all IRB findings and actions to the investigator and the institution.

iii. The procedure for expedited review does not state who is authorized to conduct the review or the method for keeping members advised of research proposals approved through expedited review. (Please refer to 21 CFR 56.110 for requirements concerning expedited review.)

iv. A requirement that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the subjects.

v. A requirement for determining which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB review.

In addition, the IRB's Written Policy references only HHS regulations under 45 CFR Part 46, and makes no reference to FDA regulations under 21 CFR Part 50 or Part 56.

2. **Failure to ensure research involving children is in compliance with Part 50, subpart D, at the time of initial review of the research. [21 CFR 56.109(h) & 21 CFR 50.50].**

The IRB failed to ensure that research involving children complied with the requirements listed in 21 CFR 50, subpart D – "Additional Safeguards for Children in Clinical Investigations." Specifically, the IRB approved Study Protocol [redacted] on March 10, 2005. Even though this study allows enrollment of subjects as young as 12 years of age, there was no documentation in the IRB's files that the regulations involving safeguards for children were discussed or ensured.

3. **Failure to ensure that the IRB reviewed proposed research at convened meetings at which a majority of the members of the IRB were present, including at least one member whose primary concerns are in nonscientific areas. [21 CFR 56.108(c)].**

This is a repeat of a violation cited in the last IRB inspection in May 2004.

You failed to ensure that, except when an expedited review procedure was used, the IRB reviewed proposed research at convened meetings at which the members present constituted a majority, including at least one member whose primary concerns were in the nonscientific areas. For example:

a.) At the November 2, 2006, IRB meeting, the minutes indicate that only five of the nine listed members of the IRB were present. Although this was a majority, the IRB minutes for the meeting note that [redacted] abstained from voting on approvals for specific studies due to a conflict of interest. Ms. [redacted] abstentions resulted in loss of the quorum, since only four of the nine members of the IRB were able to vote for these approvals. The following studies were affected:

i. Annual update and request for termination of Study [redacted]

ii. Annual update of Study [redacted]

iii. Approval of revisions for Study [redacted]

b.) The IRB approved Informed Consent Forms by "voice vote" rather than during convened meetings. The FDA investigator was informed that, for a "voice vote", each member was called individually by telephone and asked for their vote, as noted above in **cite number 1b**.

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.

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. Please send your response to:

Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Bioresearch Monitoring, HFZ-311
9200 Corporate Boulevard, Rockville, Maryland 20850
Attention: Ms. Doreen Kezer, Chief, Special Investigations Branch.

A copy of this letter has been sent to the FDA Chicago District Office, 550 W. Jackson St., Suite 1500, Chicago, IL 60661. Please send a copy of your response to that office.

If you have any questions, please contact Ms. Doreen Kezer at 240-276-0125 or at Doreen.Kezer@fda.hhs.gov.

Sincerely yours,

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

cc:

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