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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Blvd.
Rockville MD 20850

WARNING LETTER

VIA FEDERAL EXPRESS

MAY 8 2007

Sister M. Johanna DeLeys, President/CEO
St. Elizabeth Medical Center IRB
2209 Genesee Street
Utica, NY 13501

Dear Sister Johanna:

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 January 16 through January 25, 2007, by an investigator from the FDA New York District Office, as a result of which FDA is invoking administrative actions in accordance with 21 CFR 56.120, as further described below. 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, many of which repeat violations cited in a letter sent from FDA to your IRB in November 2004, as a result of an inspection conducted in April 2004.

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 follow required written procedures [21 CFR 56.108(a) & (b)].**

   Review of the inspection report indicates that the IRB failed to follow written procedures for conducting initial and continuing review of research, as required by 21 CFR 56.108(a)(1). For example:

a.) The IRB's written procedures state that "the IRB shall consist of thirteen (13) members." Since October 12, 2005, the IRB membership roster has listed only 12 members.

b.) The IRB's written procedures state "Attendance Requirements – The board members shall be required to attend at least 50% of the IRB meetings annually." The IRB's records indicate that one of the board members, [redacted], has only attended one IRB meeting out of the nine that have occurred since August 2004. There is no documentation that this violation of attendance requirements has been identified or addressed by the IRB.

c.) The IRB's written procedures state that "no member shall vote by proxy." However, the IRB minutes dated October 12, 2005, note that the [redacted] study "was approved by proxy vote until this meeting."

d.) The IRB's written procedures state that "meetings will be held on an as-needed basis, but no less than quarterly." However, the IRB records indicate that the IRB has met at intervals greater than three months on four occasions since August 2004.

e.) The IRB's written procedures for Expedited Review state that the IRB may utilize expedited review for "research involving no more than minimal risk or review minor changes in previously approved research." However, a board member, the IRB secretary, was allowed expedited review authority to grant approval for significant study changes and annual renewal of significant risk studies. For example:

- The IRB secretary granted expedited review approval on November 13, 2006, of a revised informed consent form for the [redacted] Among other things, the revised form contained a significant change in study procedures in that study subjects were now required to have "approximately [redacted] mls" of [redacted] at [redacted] different time points during the study, instead of "a [redacted] [redacted] one time as specified in the older consent form.
- The IRB secretary granted expedited review approval on December 6, 2006, for annual renewal of approval of the [redacted].

Please also note that when expedited review is used appropriately, FDA regulations at 21 CFR 56.110(b) require that authority to grant expedited review approval is given to the IRB chairman or to an experienced reviewer. The IRB secretary, who is listed as a non-scientific member of the board, may not meet the requirements for an experienced reviewer in all situations, particularly those that deal with medical concerns and risks to human subjects.

f.) The IRB's written procedures state that "all IRB members shall be informed of actions taken under expedited review within one (1) week." However, in several instances, IRB members were notified of expedited review actions weeks or months later. For example, with regard to the [redacted]:

- Expedited review and approval of study materials was granted on February 13, 2006, but IRB members were not notified until the April 12, 2006, board meeting.
- Expedited review and approval of a revised informed consent was granted on November 13, 2006, and of recruitment advertisements on November 28, 2006, but

IRB members were not notified until the December 19, 2006, board meeting.

- Expedited review and approval of renewal of the study was granted on December 6, 2006, but IRB members were not notified until the December 19, 2006, board meeting.

g.) In addition, your IRB did not follow, because it did not establish, written procedures for:

- Determining which projects require review more than once per year, as required by 56.108(a)(2).
- Ensuring prompt reporting to the IRB of changes in research activity, as required by 21 CFR 56.108(a)(3), and for ensuring 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 human subjects, as required by 21 CFR 56.108(a)(4), in that you had no procedures for review by the IRB of protocol deviations.
- Ensuring prompt reporting to the IRB, appropriate institutional officials, and FDA of any unanticipated problems involving risk to human subjects or others, as required by 21 CFR 56.108(b)(1).
- Ensuring prompt reporting to the IRB, appropriate institutional officials, and FDA of any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB, as required by 21 CFR 56.108(b)(2), insofar as you did not have or follow procedures to ensure that clinical investigators comply with IRB conditions of approval. For example, the IRB's December 14, 2005, initial approval letter for the [redacted] required "a progress report in [redacted] months, which includes the number of subjects enrolled and any information regarding clinical outcomes." The only progress report found in the IRB files for this study was a letter from the clinical investigator dated August 7, 2006 designated as a "rough draft" and which stated "should not be incorporated into the medical record." There was no documentation of any action taken regarding this progress report being submitted two months late, or of a request for a final version of the letter.

2. **Failure to use expedited review procedures only for certain kinds of research involving no more than minimal risk or for minor changes in approved research [21 CFR 56.110].**

The IRB granted approval by expedited review of research for significant risk studies that did not meet the criterion of minimal risk or minor changes in approved research. For example:

a.) As noted above in **citation 1e**, the IRB secretary granted expedited review approval on November 13, 2006, of a revised informed consent form for the [redacted], which contained a significant change in study procedures.

b.) The IRB secretary granted expedited review approval on December 6, 2006, for annual renewal of approval of a significant risk study, the [redacted].

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. [21 CFR 56.108(c)].**

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. Specifically, use of the [redacted] was renewed on August 22, 2005, by a "paper ballot" or "proxy" vote, in which IRB members received a ballot by mail to vote on renewal of the study for one year.

4. **Failure to prepare and maintain adequate documentation of IRB activities [21 CFR 56.115(a)].**

   The IRB's records are inaccurate and/or incomplete. For example:

   a.) Copies of all research proposals reviewed have not been maintained. Specifically, the [redacted] was approved for renewal on October 12, 2005, and again on June 14, 2006. However, the IRB files contained no record of the proposals or documents that were reviewed for the study.

   b.) Minutes of IRB meetings are inaccurate or incomplete. Specifically:

   - The June 14, 2006, IRB meeting minutes document the presentation of a revised protocol for the [redacted]. However, the minutes of that meeting contain no record of action on this protocol revision. There is no mention of this protocol at the next IRB meeting on October 13, 2006, suggesting that it was addressed at the June meeting.
   - The October 13, 2006, IRB meeting minutes document the approval of the [redacted] with a vote of 6 to approve and 1 abstaining. However, the IRB minutes note that 8 IRB members were present, but only 7 votes are accounted.

5. **Failure to conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year [21 CFR 56.109(f)].**

   The IRB granted approval of for use of a significant risk device for a period of greater than one year. Specifically, on June 14, 2006, the IRB voted to renew the approval for the [redacted] through October 12, 2007, a period of [redacted] months.

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.

Moreover, our review of the recent inspection report indicates that the IRB's present failure to comply with continuing review, expedited review, records, and written procedure requirements, repeats and continues violations found during the April 2004 inspection and reflected in FDA's November 15, 2004, letter to you. Also, the IRB has not taken all of the corrective and preventative actions promised after that 2004 inspection and letter, to assure future compliance with FDA regulations.

As we indicated in the letter issued in November 2004, noted deviations were not intended to **be** an all-inclusive list of deficiencies that may exist at the IRB. It is your responsibility to assure that the St. Elizabeth Medical Center IRB adheres to each requirement of the Federal Food, Drug, and Cosmetic Act (21 USC 321) and all applicable FDA regulations.

As a result of the IRB's ongoing non-compliance with FDA regulations, described above, in accordance with 21 CFR 56.120(b)(l) and (2), FDA hereby notifies you that it may withhold approval of new studies subject to 21 CFR Part 56 that are reviewed by your IRB. In addition, we are directing that **no new subjects** be enrolled into ongoing studies subject to 21 CFR Part 56. These restrictions will remain in effect until FDA has evidence of adequate corrective actions and notifies you in writing that the IRB's corrective actions are satisfactory.

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 will result in the continuation of the restrictions described above and could result in the FDA taking further regulatory action, including the initiation of disqualification proceedings in accordance with 21 CFR 56.121. 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 New York District Office, 158-15 Liberty Avenue, Jamaica, NY 11433. 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,

Larry D. Spears for

Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and
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cc:

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