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Inspections, Compliance, Enforcement, and Criminal Investigations

Marquette General Health System IRB 1/18/11



Department of Health and Human Services

Public Health Service
Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-0002

WARNING LETTER

JAN 18 2011

VIA UPS EXPRESS

A. Gary Muller, FACHE
President and Chief Executive Officer
Marquette General Health System
580 W. College Avenue
Marquette, MI 49855

Dear Mr. Muller:

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 October 18, 2010, to October 21, 2010, by investigators from the FDA Detroit 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 and discusses your written response dated November 8, 2010, to the noted violations.

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 violations of Title 21, Code of Federal Regulations (21 CFR) Part 812-Investigational Device Exemptions, Part 50-Protection of Human Subjects, Part 56-Institutional Review Boards, and Section 520(g) (21 USC 360j(g)) of the Federal Food, Drug, and Cosmetic Act (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 Form FDA 483, your written response, and our subsequent review of the inspection report are discussed below:

Failure to require that information given to subjects as part of informed consent is in accordance with 21 CFR 50.25. [21 CFR 56.109(b)]

An IRB shall require that information given to subjects as part of informed consent is in accordance with 21 CFR 50.25. On November 12, 2008, your IRB approved a revised informed consent document for the **(b)(4)** Randomized Clinical Study," which lacked the following required information:

- identification of any procedures which are experimental;

- an explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights;
- a statement that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled;
- a statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable; and
- a statement informing subjects that significant new findings which may relate to the subject's willingness to continue participation will be provided.

Your written response states that effective December 1, 2010, all informed consents will be reviewed against 21 CFR 50.25 by the IRB committee members at the time of approval and appropriately documented in the minutes and correspondence to principal investigators. Your response also states that Marquette General Hospital (MGH) IRB Policy #2 "Elements of Informed Consent" will be revised to correspond with 21 CFR 50.25.

Your response is inadequate in that you did not sufficiently describe and submit any revisions to IRB policies and procedures, or training provided to IRB staff on the revised policy and procedures. In your response to this letter, please provide the revised IRB Policy, any revised procedures, documentation of the training staff has received on the new policies and procedures, and the Informed Consent Checklist.

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

An IRB shall follow written procedures for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution.

Your IRB failed to follow its continuing review procedure, MGH IRB Procedure #2, which requires that a written progress report be submitted to and reviewed by the IRB. Specifically, the February 12, 2010, e-mail request to continue the **(b)(4)** trial and March 10, 2010, meeting minutes and approval letter indicate that the IRB approved continuation without a progress report.

Your written response states that effective December 1, 2010, Procedure #2 – "Procedures for Continuing Review by the IRB" will be revised to require a Renewal Form to be completed by all principal investigators. The completed form must be submitted to the IRB secretary by the due date along with a copy of the current informed consent form (if applicable) used for the study.

Your response is inadequate in that you did not provide assurance that the revised procedure will be followed. In addition, the Renewal Form should include a question as to whether there were any changes to the protocol. In your response to this letter, please provide the revised procedure, Renewal Form, and documentation of the training IRB staff has received on the new procedure.

Failure to include at least one member whose primary concerns are in a nonscientific area when reviewing proposed research at convened meetings. [21 CFR 56.108(c)]

Except when an expedited review procedure is used, each IRB shall review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas.

Minutes of the September 2010 meeting indicate that your IRB voted on FDA-regulated research without at least one member whose primary concerns are in nonscientific areas in attendance. Specifically, your IRB approved the protocol, consent form, Quality of Life form, investigator's brochure, and package insert pertaining to the **(b)(4)** study.

Your written response states that you have recruited an additional nonscientific member to ensure a quorum. Your response is inadequate in that you did not discuss any procedures that have been developed to ensure membership requirements will be followed when the IRB meets to review and approve research. In your response to this letter, please submit a copy of the procedures for ensuring compliance with IRB membership requirements, as well as documentation of training IRB staff has received on the procedure.

Failure to prepare and maintain adequate documentation of IRB activities, including minutes of IRB meetings. [21 CFR 56.115(a)(2)]

An IRB shall prepare and maintain adequate documentation of IRB activities, including minutes of IRB meetings, which shall be in sufficient detail to show attendance at the meeting; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution. Examples of your failure to adhere to this regulation include, but are not limited to, the following:

- The November 8, 2006, meeting minutes do not document an evaluation of the nonsignificant risk classification of the **(b)(4)** study prior to the IRB approving the study.
- The May 9, 2007, meeting minutes do not document a review of the adverse events that were reported

for the **(b)(4)** implant study prior to the IRB approving continuation of the study.

Your written response states that effective December 1, 2010, the IRB minutes will specifically document any discussions had by the Board regarding issues and actions that were taken. Your response is inadequate in that you have not provided corrective actions to prevent this deviation from reoccurring. Please provide any procedures for preparing meeting minutes, records of training staff has received on them, and dates of implementation.

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 additional 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.

Your response should reference "CTS # EC100608/E001" and be sent to:

Attention: Anne T. Hawthorn, J.D.
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance
Division of Bioresearch Monitoring
10903 New Hampshire Avenue
Building 66, Room 3504
Silver Spring, Maryland 20993-0002.

A copy of this letter has been sent to the Detroit District Office, 300 River Place, Suite 5900, Detroit, MI 48207-4291. Please send a copy of your response to that office.

The Division of Bioresearch Monitoring has developed introductory training modules in FDA regulated device clinical research practices, which are available on the FDA website. The modules are for persons involved in FDA regulated device clinical research activities. These modules are located at the following website address:

<http://www.fda.gov/Training/CDRHLearn/ucm162015.htm>¹.

If you have any questions, please contact Anne T. Hawthorn, (301) 796-6561, Anne.Hawthorn@fda.hhs.gov.

Sincerely yours,

/s/

Steven D. Silverman
Director
Office of Compliance
Center for Devices and
Radiological Health

Links on this page:

1. <http://www.fda.gov/Training/CDRHLearn/ucm162015.htm>