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Inspections, Compliance, Enforcement, and Criminal Investigations

[REDACTED] IRB 1/10/14



Department of Health and Human Services

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

January 10, 2014

WARNING LETTER

VIA UNITED PARCEL SERVICE



Dear Ms. [REDACTED]:

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 May 6, 2013, to June 13, 2013, by an investigator from the FDA Chicago District Office. This inspection was conducted 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 (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 IRB's written response dated June 27, 2013, 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 applications, and Premarket Notification submissions 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 21 CFR Part 56 - Institutional Review Boards, which concern requirements prescribed under section 520(g) of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. § 360j(g). 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 IRB's written response, and our subsequent review of the inspection report, are discussed below:

1. Failure to follow written procedures for conducting an 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. The January 2012 Mercy Hospital & Medical Center (MH&MC) IRB Policy and Procedure Manual (SOP) states, "investigators must have an investigational device exemption (IDE) application on file with FDA and have

received an IDE number." In addition, the SOP also requires that Clinical Investigators include the name of the device, IDE#, and name of the company manufacturing the device on the protocol submission form. Moreover, a copy of the FDA approval letter must be included in the protocol submission form. Your IRB conducted the initial and continuing reviews of FDA-regulated research studies subject to IDE approval. However, your IRB reviewed and approved protocols that did not include the IDE information required by your SOP. Specifically, the following clinical investigations of significant risk investigational devices did not contain the relevant IDE application number or FDA approval letter in their submission forms:

a) **(b)(4)**

b) **(b)(4)**

It is essential that IRBs follow their written procedures when conducting initial and continuing review of FDA-regulated research studies. This ensures that the IRB's review of research is conducted completely and adequately. Not adhering to the above regulation could expose study subjects to risk of harm and potentially compromise the scientific integrity and reliability of research data submitted in support of marketing applications.

2. Failure to review proposed research at convened meetings at which a majority of the members of the IRB are present. [21 CFR 56.108(c)]

Except when an expedited review procedure is used, an IRB is required to review proposed research at its convened meetings with a majority of the members present, including at least one member whose primary concerns are in nonscientific areas. Your IRB reviewed FDA-regulated research when less than a majority of the members were present. Examples of this deviation include, but are not limited to, the following:

a) **(b)(4)**

b) **(b)(4)**

In order to adequately review research, the IRB must ensure that a majority of IRB members are present at a convened meeting. This helps to ensure that members with the necessary diversity and expertise are present to evaluate proposed research. In addition, having a majority of the voting members present at the meeting is important to safeguarding the rights and welfare of human subjects and ensuring complete and adequate review of research activities.

3. Failure to prepare and maintain required written procedures governing the function and operations of the IRB. [21 CFR 21 CFR 56.115(a)(6) and 56.108(a)(1)-(2)]

An IRB must prepare and maintain written procedures for conducting its initial and continuing review of research and reporting its findings and actions to the investigator and the institution. IRBs must also prepare and maintain written procedures for determining which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB review. Examples of the failure to prepare and maintain written procedures required by 21 CFR 56.108(a) include the following:

a) Your IRB's January 2012 IRB Policy and Procedure Manual has no written procedures for determining which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB review.

b) Your IRB's January 2012 IRB Policy and Procedure Manual lacked procedures for reporting its findings and actions to the institution.

This helps to ensure that research is appropriately reviewed, thereby protecting the safety and welfare of research subjects. The procedure for reporting your IRB's findings to the institution ensures that the institution is aware of issues that may impact or require follow-up action.

4. Failure to retain IRB records for at least 3 years after completion of the research. [21 CFR 56.115(b)]

An IRB shall retain the records required by 21 CFR 56.115(a) for at least 3 years after completion of the research, and the records shall be accessible for inspection and copying by authorized representatives of the Food and Drug Administration at reasonable times and in a reasonable manner. Examples of your IRB's failure to adhere to this regulation include, but are not limited to, the following:

- a) Rosters of IRB membership prior to (b)(4) have not been retained;
- b) IRB meeting minutes from meetings held (b)(4) and (b)(4), have not been retained;
- c) The study "(b)(4)" was approved on (b)(4), but the research proposal has not been retained;
- d) Copies of Policies and Procedures prior to (b)(4), have not been retained.

Retaining IRB rosters, meeting minutes, and written policies and procedures is an important part of IRB activities in that it provides documentation of IRB membership and activities, including documenting the members who were present at IRB meetings and approved certain research activities.

5. Failure to prepare and maintain adequate documentation of IRB activities including minutes of IRB meetings that are of sufficient detail to show the actions taken at the meeting and the vote on these actions. [21 CFR 56.115(a)(2)]

An IRB must prepare and maintain minutes of IRB meetings that shall be of sufficient detail to show attendance at the meetings; 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 of research; and a written summary of the discussion of controverted issues and their resolution. An example of your IRB's failure to maintain minutes that show the vote or the actions taken by the IRB is:

On (b)(4), the IRB reviewed and approved the study "(b)(4)" with modification, but there is no vote count included in the minutes.

The citations listed above appear to be an on-going problem as several of these citations are repeat violations identified during the FDA inspection conducted in 2002.

Your IRB's written response states that the IRB's corrective action plan includes the following: the development of a "children's" specific checklist for all IRB members to ensure full board deliberation and determination of compliance with 21 CFR Part 50 Subpart D; and providing a checklist for the Medical IRB members prompting review of SR/NSR determination to ensure full board deliberation and determination of compliance with 21 CFR 56.108. Your IRB's response also indicates that it revised processes to include a sample of factors that may be considered in determining which projects require verification from sources other than the investigator to confirm that no material changes have occurred since the previous IRB review; to ensure that a majority of members are present, including at least one member whose primary concern is non-scientific; and for reporting the IRB's findings and action to the institution. The IRB's response also states that it will be putting in place a threefold process for conducting its initial review of research. Your IRB's response also proposes corrective actions to ensure that all future IRB documents are maintained and include additional processes to ensure that investigators submit close-out reports once all study related activities have been completed.

The response is inadequate because it does not describe any process that the IRB will use to train and educate IRB members, staff, and clinical investigators with respect to its revised written procedures and checklists, nor does it provide projected implementation and completion dates. Without this information, FDA cannot conduct an informed evaluation of the proposed corrective and preventive actions' potential ability to prevent the recurrence of these or similar violations in the future.

Please submit a copy of your IRB's written procedures, or any draft procedures in development, and a timeline for the implementation of new/revised procedures. In addition, please provide a description of any training provided to IRB staff on the new/revised procedures and a list of attendees, or a projected timeline of planned training.

The violations described above are not intended to be an all-inclusive list of problems that may exist at

your IRB. You are responsible for ensuring compliance with the Act and applicable regulations.

We also note that under 21 CFR 56.111(c), IRBs are required to review clinical investigations involving children as subjects to ensure compliance with 21 CFR Part 50 Subpart D and approve only those clinical investigations that satisfy the criteria within certain risk categories identified in 21 CFR sections 50.51, 50.52, or 50.53. Your IRB's meeting minutes do not reveal whether your IRB determined the risk categories for these clinical investigations involving children and whether the criteria for the applicable category were met. Children participating in research represent a vulnerable population and require additional safeguards to ensure their safety and welfare. It is important to conduct an initial review in accordance with FDA's regulations to avoid potentially placing these children at increased risk of harm and to better protect their rights as study subjects.

Further, we note that your IRB's protocol states that "investigators should terminate a protocol when human subjects are no longer being followed or studied. As long as subjects (patients or otherwise) are still being followed at this site, even if the protocol is closed to subject accrual, or if data is still being analyzed even if not being actively collected, a protocol is considered active and continuing review must be completed. If no subjects are being followed and data analysis is complete, the study may be officially terminated. When research has been terminated, the responsible investigator must inform the IRB. Investigators are encouraged to notify the IRB as soon as a study is terminated." Your IRB's status charts for the studies that you review and approve should be maintained and updated to identify whether a study is active, terminated, or another appropriate status.

Within 15 working days of receiving this letter, please provide documentation of the additional actions that you have taken or will take to correct these violations, to prevent the recurrence of similar violations, and to plan to monitor the effectiveness of your corrective actions. 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 # EC120619/E001" and be sent to:

Attention: Veronica J. Calvin, M.A.
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance
Division of Bioresearch Monitoring
10903 New Hampshire Avenue
Building 66, Room 3508
Silver Spring, Maryland 20993-0002.

A copy of this letter has been sent to FDA's Chicago District Office, 550 W. Jackson, Suite 1500, Chicago, IL 60661. 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 Veronica Calvin at (301) 796-5647 or Veronica.Calvin@fda.hhs.gov.

Sincerely yours,
/S/
Steven D. Silverman
Director
Office of Compliance
Center for Devices and
Radiological Health

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