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## Inspections, Compliance, Enforcement, and Criminal Investigations

[REDACTED] 8/1/13



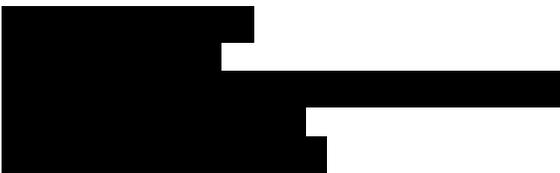
Department of Health and Human Services

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

August 1, 2013

### WARNING LETTER

#### VIA UNITED PARCEL SERVICE



Dear Dr. [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 April 17, 2013, to April 22, 2013, by an investigator from the FDA Detroit 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 April 23, 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, 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 concerns 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 prepare, maintain, and follow written procedures for conducting initial and continuing review of research [21 CFR 56.108(a) and 56.115(a)(6)]**

An IRB must prepare, maintain, and follow written procedures for its review of research and for reporting its findings and actions to the investigator and the institution. Examples of these failures include, but are not limited to, the following:

- a. The section of your IRB's SOPs titled "Medical Investigational Device Determinations" outlines procedures for making Significant Risk (SR) or Non-Significant Risk (NSR) determinations during initial review of device studies. These procedures include a requirement that "minutes of IRB meetings must document the rationale for SR/NSR and subsequent approval or disapproval decisions for the clinical investigation." However, your IRB failed to document the SR/NSR rationale in its meeting minutes from January 14, 2013, for the approval of the NSR study titled "A Double-Blinded, Randomized, Sham-Controlled, Proof of Concept Phase 2 Study Exploring the Safety and Efficacy of RINCE Technology for the Treatment of Patients with Fibromyalgia PERRFECT-SJMO Prospective Evaluation of RINCE to Reduce Fibromyalgia Effects." This is a significant violation because the risk determination is an essential element of the review of FDA-regulated medical device studies by IRBs. Therefore, it is critical that IRBs follow their written procedures for the SR/NSR determination in initial review of studies, including their procedures for documentation of the process in meeting minutes.
- b. Your IRB's SOPs lack procedures for reporting its findings and actions to the institution.
- c. Your IRB failed to follow its written procedures related to continuing review. Specifically, for the study titled "Pivotal Trial to Evaluate the Safety and Efficacy of the Diamondback 360° Orbital Atherectomy System in Treating De Novo, Severely Calcified Coronary Lesions (ORBIT II)," the IRB approved the previous continuing review on April 10, 2012, and set the next renewal due date as April 8, 2013. Your IRB received a renewal form for this study on March 25, 2013, but failed to review it prior to the study's approval expiring.

It is critical that your IRB maintain and follow its written procedures for the review of research. This helps to ensure that research is appropriately reviewed and that findings are reported to the institution, and to protecting the safety and welfare of research subjects. Reporting ensures that the institution is aware of issues that may impact it or require follow-up action. In addition, continuing review is a critical method in ensuring that research is continuing to be conducted appropriately. Non-compliance with the above regulations and your IRB's SOPs may expose research subjects to a significant risk of harm, damage the scientific integrity and usefulness of research data collected, and adversely impact ethical principles governing research.

Your IRB's response states that discussions surrounding the agreement or disagreement of an NSR determination will be documented in the meeting minutes. Your IRB's response also states that your IRB will report its activities through the meeting minutes to the institution's Quality and Safety Committee of the Board of Trustees on a monthly basis. In addition, the IRB will maintain a database of continuing review dates for the studies it oversees and will conduct emergency meetings when necessary to meet continuing review deadlines.

Your IRB's response is inadequate in that it does not sufficiently describe the new reporting and continuing review procedures and plans for training IRB staff on these procedures. In your response to this letter, please provide a copy of the updated IRB SOPs and documentation showing that appropriate staff have been trained.

## **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 pursuant to 21 CFR 56.110, in order for an IRB to review proposed research at its convened meetings, the IRB is required to have a majority of its 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 deficiency include, but are not limited to, the following:

- a. On February 13, 2012, your IRB failed to meet with a majority in that only (b)(4) of (b)(4) members were present; however, your IRB's meeting minutes indicate that your IRB reviewed and approved renewal of the study titled "Thrombectomy Revascularization of large Vessel Occlusions in Acute Ischemic Stroke (TREVO 2)."
- b. On July 9, 2012, your IRB failed to meet with a majority in that only (b)(4) of (b)(4) members

were present; however, your IRB's meeting minutes indicate that your IRB reviewed and approved renewal of the study titled "Vitesse Intracranial Stent Study for Ischemic Therapy."

In order to adequately review research, continuing review of significant risk device research should only be performed when a majority of IRB members is present. This helps to ensure that members who have the necessary diversity and expertise can evaluate any changes in the research including new risks to subjects. In doing so, the IRB ensures that determinations regarding risks, potential benefits, informed consent, and any modifications or new information is adequately considered to protect research subjects. Not doing so can place human subjects' safety at risk.

Your IRB's response states that your IRB will ensure a quorum is present prior to conducting any business and that your IRB's Standard Operating Procedures (SOPs) define a quorum as "a majority (more than ½) of the voting members." The response also clarified that these members must be physically present or present via phone communication and that e-mail voting will no longer be allowed.

Your IRB's response is inadequate in that it does not sufficiently describe the new quorum procedures and plans for training IRB staff on these procedures. In your response to this letter, please provide a copy of the updated IRB SOPs and documentation showing that appropriate staff members have been trained.

### **3. Failure to report promptly to the FDA any suspension or termination of approval and failure to prepare written procedures [21 CFR 56.113 and 21 CFR 56.115(a)(6)]**

An IRB has the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination must be reported promptly to the investigator, appropriate institutional officials, and the FDA. An IRB must also prepare and maintain written procedures for the IRB as required by 21 CFR 56.108(b). Your IRB failed to report to the FDA the February 22, 2010, suspension of approval for (b)(4) use of the (b)(4).

It is essential that an IRB has procedures in place for ensuring such reporting to the FDA. An IRB's prompt reporting of suspensions and terminations of research approval to the FDA allows the Agency to fully evaluate and quickly address potential problems in FDA-regulated research, including potentially serious safety issues.

Your IRB's response states that Serious Adverse Events occurring in FDA-regulated research projects will be reported to the FDA within 10 business days. In addition, all suspensions and terminations will be reported to the institution's Quality and Safety Committee of the Board of Trustees and the FDA within 10 business days.

Your IRB's response is inadequate in that it does not sufficiently describe the reporting procedures and plans for training IRB staff on these procedures. In your response to this letter, please provide a copy of the updated IRB SOPs and documentation showing that appropriate staff members have been trained.

### **4. 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)]**

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.

Your IRB's member lists from March 12, 2012, to the date of the inspection failed to properly identify the relationship between each member and the institution.

Without the presence of an updated member list showing the relationship between each member and the institution, an IRB cannot adequately demonstrate that its membership includes at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution, as required by 21 CFR 56.107(d). Maintaining an updated list of the IRB members' institutional affiliation is important to ensure the IRB's review of research is fair and equitable. It would also prevent the participation of any member who may have a conflict of interest.

Your IRB's response states that your IRB will maintain a file identifying the relationship of IRB members with the institution.

Your IRB's response is inadequate in that it does not provide documentation showing that the member list has been corrected or sufficiently describe plans for maintenance of this information. In your response to this letter, please provide a copy of the corrected member list. Please also provide updated IRB SOPs and documentation of training addressing maintenance of this information.

The FDA investigator also observed during the inspection that your IRB's List of Active Studies was not complete and current. Specifically, several studies on this list had expired dates or no dates at all in the Pending Renewal Dates column. We would like to take this opportunity to remind your IRB of the importance of maintaining a study list with current and accurate information on the studies it is responsible for overseeing.

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 15 working days of receiving this letter, please provide documentation of the actions that you have taken or will take to correct these violations and to prevent the recurrence of similar violations, and a 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 # EC130153/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 Detroit District Office, 300 River Place, Suite #5900, Detroit, MI 48207. 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><sup>1</sup>.

If you have any questions, please contact Veronica Calvin at (301) 796-5647 or [Veronica.Calvin@fda.hhs.gov](mailto:Veronica.Calvin@fda.hhs.gov).

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

cc:

Michael K. Smith, D.O.  
IRB Chair  
Vice President of Medical Affairs & Chief Medical Officer  
St. Joseph Mercy Oakland Health System