

APR 3 2007

WARNING LETTER

VIA FEDERAL EXPRESS

Thomas P. Davis, M.D.
St. John Hospital and Medical Center
Cardiology Division
22101 Moross Road
Detroit, MI 48236

Dear Dr. Davis:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection conducted at your clinical site from November 20 to December 12, 2006 by an investigator from the FDA Detroit District Office. The purpose of this inspection was to determine whether your activities as both sponsor and investigator in clinical studies using the [redacted] and [redacted] for [redacted] complied with applicable federal regulations. The [redacted] and the [redacted] are devices as that term is defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 321(h). This letter also requests prompt corrective action to address the violations cited and discusses your written response 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 serious violations of Title 21, Code of Federal Regulations (21 CFR) Part 812 -- Investigational Device Exemptions. 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:

- 1. Failure to submit an application to FDA for use of a significant risk device in an investigation and failure to obtain FDA's approval prior to beginning an investigation for which an FDA-approved IDE was required [21 CFR 812.20(a)(1) and 812.20(a)(2)].**

Pursuant to 21 CFR 812.20(a)(1) and 812.20 (a)(2), a sponsor shall submit an application to the FDA if the sponsor intends to use a significant risk device as defined by 21 CFR 812.3. Furthermore, a sponsor shall not begin an investigation for which an IDE is needed, until FDA has approved the application. Examples of your failure to adhere to the above stated regulation include, but are not limited to, the following:

You acted as both sponsor and clinical investigator in The [redacted] Protocol. This study used the [redacted] and the [redacted] and [redacted] System; and the [redacted] and [redacted] Systems in the treatment of [redacted]. As a sponsor, you are required to obtain a new IDE if a device that is approved for one indication is intended to be used in a clinical study for a new indication.

The [redacted] was implanted into 37 subjects, the [redacted] was implanted into six subjects, the [redacted] was implanted into seven subjects, the [redacted] was implanted into 17 subjects, and one subject was implanted with [redacted].

Your written response states that you were not aware that an IDE was required for an FDA-approved [redacted] to be used off-label, that there was no assessment of degree of risk from the IRB, and that you were not aware that you met the definition of a sponsor-investigator. Your response also states that when it was discovered that an IDE was required, one was submitted. We note that the IDE that you submitted requested **retrospective** approval, and you have been notified that your request was not approved. Please note that your protocol, informed consent documents, and case report forms clearly demonstrate that these subjects were enrolled as part of your clinical trial, not participants in "off-label use" of an approved device. Your response is inadequate in that it does not address how this deficiency will be avoided in the future. Please submit a corrective action plan that addresses how you plan to prevent this deviation from occurring in future studies.

2. Failure to obtain a signed investigator agreement from each participating investigator [21 CFR 812.43(c)].

Pursuant to 21 CFR 812.43(c), a sponsor is responsible for obtaining a signed investigator agreement from each participating investigator. Examples of your failure to adhere to the above stated regulation include, but are not limited to, the following:

You did not obtain signed investigator agreements from any of the twelve physicians who implanted investigational devices into subjects or provided medical evaluations and/or assessments of subjects enrolled, as follows:

A. You did not sign an investigator agreement; however, you were the clinical investigator and surgeon for the investigational device implantation procedure for approximately 38 subjects. Examples include, but are not limited to:

Subject [redacted]
Subject [redacted]
Subject [redacted]

B. Dr. [redacted] did not sign an investigator agreement; however, he was the clinical investigator and surgeon for the investigational device implantation for approximately 30 subjects. Examples include, but are not limited to:

Subject [redacted]
Subject [redacted]
Subject [redacted]

C. As stated above, neither you nor Dr. [redacted] signed investigator agreements; however you were co-investigators/surgeons for the investigational device implantation for approximately six subjects. Examples include, but are not limited to:

Subject [redacted]
Subject [redacted]
Subject [redacted]

D. [redacted] M.D., did not sign an investigator agreement; however, he was the clinical investigator and surgeon for the investigational device procedure for subject [redacted] and subject [redacted]

E. [redacted] M.D., did not sign an investigator agreement; however, he was the primary operator for the implantation procedure for subject [redacted]

Your written response states that you and your staff will attend an FDA-sponsored device-related program to improve understanding of investigator-sponsor roles and responsibilities, that departmental standard operating procedures (SOPs) have been revised to include a policy and procedure for investigator-sponsored device studies, and that the failure to obtain investigator agreements will be reported to the IRB and will be completed for all investigators where possible. Your response is inadequate in that it does not provide a timeline for these activities, the name of the training program referred to in your response, a copy of the revised SOP, and a copy of the notification to the IRB. Please provide this information in order to address this deficiency.

3. Failure to ensure proper monitoring of the investigation [21 CFR 812.40].

Pursuant to 21 CFR 812.40, a sponsor is responsible for ensuring proper monitoring of the investigation. Examples of your failure to adhere to the above stated regulation include, but are not limited to, the following:

Although the protocol designated [] Ph.D., and [] Ph.D., as individuals to act as Safety Data/Monitoring personnel, there is no documentation of monitoring during the clinical trial by either individual, or by any designee, for the period [] through []

Your written response states that all present and future studies in which the investigator is also the sponsor will have appropriate monitoring, that you have educated your staff regarding investigator-sponsor roles and responsibilities in the monitoring of device studies, and that you will attend an available FDA program on devices for additional education. Your response is inadequate in that it does not provide the policies and procedures you have put into place to ensure appropriate monitoring of clinical studies. Please provide these policies and procedures as well as a timeline for these activities and the name of the training program referred to in your response.

4. Failure to maintain records of shipment and disposition to include the name and address of the consignee, type and quantity of device, date of shipment, and batch number or code mark [21 CFR 812.140(b)(2) and 812.140(a)(2)(i)].

Pursuant to 21 CFR 812.140(b)(2), a sponsor shall maintain accurate, complete and current records of shipment and disposition to include the name and address of the consignee, type and quantity of device, date of shipment, and batch number or code mark. Pursuant to 21 CFR 812.140(a)(2)(i), clinical investigators shall maintain accurate, complete, and current records of receipt, use or disposition of a device that relate to the type and quantity of the device, dates of receipt and batch number or code mark. Examples of your failure to adhere to the above stated regulations include, but are not limited to, the following:

There are no records of the receipt and disposition of the investigational [] devices which you obtained from various manufacturers throughout the clinical trial. In addition, there are no records of accountability for the investigational [] devices you used to treat more than 80 subjects or for at least five of the devices that failed to deploy during the procedure.

Your response to the above violation and to the Form FDA 483 item 6 states there were no shipments of the device specifically for the trial and that the devices were shelf stock. Your corrective action plan includes training and revision of SOPs. In addition, your response states that all present and future studies involving a sponsor-investigator will have such records for devices and/or for investigational medication trials. Your response is inadequate in that you have not provided documentation of these corrective actions. As mentioned above, please provide a timeline for these activities and the name of the training program referred to in your response. In addition, please provide the SOPs you have developed to ensure that records of investigational products will be maintained according to the above stated regulation.

5. Failure to ensure that an investigation is conducted according to the investigational plan and applicable regulations [21 CFR 812.100].

Pursuant to 21 CFR 812.100, clinical investigators are responsible for ensuring that an investigation is conducted according to the investigational plan and applicable FDA regulations, for protecting the rights, safety, and welfare of subjects under the investigator's care, and for control of devices under investigation. Examples of your failure to adhere to the above stated regulation include, but are not limited to, the following:

A. According to the [redacted] Protocol inclusion/exclusion criteria, subjects that were enrolled in other current research studies were not eligible for enrollment. The following subjects were enrolled in other clinical trials prior to enrollment in the [redacted] study, and were participating in follow-up:

Subject [redacted] was enrolled and implanted in the [redacted] Trial on [redacted] and enrolled and implanted in the [redacted] Study on [redacted]

Subject [redacted] was enrolled and implanted in the [redacted] Trial on [redacted] and the [redacted] Study on [redacted]

Subject [redacted] was enrolled and implanted in the [redacted] Trial on [redacted] and the [redacted] Study on [redacted]

Subject [redacted] was enrolled and implanted in the [redacted] Trial on [redacted] and the [redacted] Study on [redacted]

B. According to the [redacted] Trial protocol inclusion/exclusion criteria, subjects cannot be enrolled in any current ongoing research study. The following subjects were enrolled in other clinical trials prior to enrollment in the [redacted] Trial, and were participating in follow-up:

Subject [redacted] was enrolled and implanted in the [redacted] Study on [redacted] and was enrolled and implanted in the [redacted] Trial on [redacted]

C. The [redacted] Protocol inclusion criteria require that the subject have $\geq 70\%$ [redacted] in the [redacted] Twelve subjects were implanted with the investigational device(s) in the **common** [redacted] although the procedure identifies the procedure for the **internal** [redacted] These subjects include, but are not limited to:

Subject [redacted] was implanted on [redacted] with a 10x30 [redacted] device

Subject [redacted] was implanted on [redacted] with a 10x30 [redacted] device

Subject [] was implanted on [] with a 10x30 [] device

Your written response states that in the future, all subjects will be carefully screened for all inclusion/exclusion criteria specific to each protocol to prevent subjects from being recruited into mutually exclusive protocols. Your response is inadequate in that it does not mention what procedures have been developed regarding how protocol deviations will be determined, documented, and reported. Your response further states that research staff, on behalf of the investigator, will attend the [] IRB-sponsored program on Informed Consents scheduled for January 25, 2007. Please clarify whether you participated in this training. In addition, please provide additional information regarding this training, i.e., title of the training and course content. Please ensure that all training is documented.

Your written response to Form FDA 483 item 4 states that all present and future studies involving a sponsor-investigator will have appropriate monitoring and that you have educated your staff regarding sponsor-investigator roles and responsibilities in the monitoring of device studies. Please note that 21 CFR 812.43(d) requires sponsors to select monitors qualified by training and experience to monitor the investigation in accordance with FDA regulations. Two individuals were designated as monitors for the clinical trial. However, during the inspection there was no information available regarding their qualifications, training, or experience in monitoring clinical studies. Your response does not address what your specific qualifications for selecting monitoring personnel are, including what training and experience is required in order for an individual to be considered qualified. Please explain what actions you have taken or plan to take to satisfy the requirements of 21 CFR 812.43(d).

Your written response to the Form FDA 483 items 8, 9, and 10 states that protocol deviations will be completed, placed in the file, and submitted to the IRB for the subjects implanted under compassionate use. In addition, your response states that all verbal requests for compassionate use will be followed by a formal written request from the investigator in order to elicit a formal authorization from the IRB. Please note that before compassionate use occurs, a sponsor should submit an IDE supplement requesting approval prior FDA approval, per 21 CFR 812.35(a). The investigator should not treat such patients until the FDA approves the use of the device under the proposed circumstances. The IDE supplement should include the patient protection measures that will be followed, i.e., informed consent. Your response is inadequate in that it does not address how this deficiency will be avoided in the future. Please provide the SOPs you have developed that describe procedures for compassionate use, to include the submission of an IDE supplement and informed consent procedures.

Your written response to Form FDA 483 item 11 states that current and future studies will utilize (when necessary) a complete informed consent form that a certified translator will convert to language understandable by the subject, according to FDA regulations. In addition, your response states that a protocol deviation will be completed and submitted to the IRB for subject [] who is a native of [] and not conversant in English. Finally, your response states that, on your behalf, the research staff will attend the IRB-

sponsored program on informed consents held January 25, 2007. Your response to this deficiency appears adequate.

The violations described above are not intended to be an all inclusive list of problems that may exist with your clinical study. It is your responsibility as a sponsor/investigator to ensure compliance with the Act and applicable regulations.

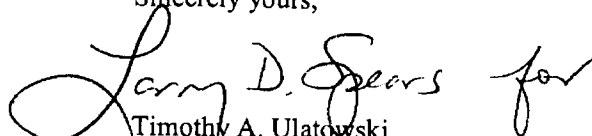
Within fifteen (15) working days of receiving this letter, please provide written documentation of the additional corrective actions you have taken or will take to correct these violations and prevent the recurrence of similar violations in current or future studies for which you are the clinical investigator. In addition, please provide a complete list of all clinical trials in which you have participated for the last five years, including the name of the study and test article, the name of the sponsor, the number of subjects enrolled, and the current status of the study. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you. In addition, FDA could initiate disqualification proceedings against you in accordance with 21 CFR 812.119.

You will find information to assist you in understanding your responsibilities and planning your corrective actions in the FDA Information Sheets Guidance for Institutional Review Boards and Clinical Investigators, which can be found at <http://www.fda.gov/oc/ohrt/irbs/>. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. Send your response to: Attention: Doreen Kezer, Chief, Special Investigations Branch, Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, 9200 Corporate Boulevard, HFZ-310, Rockville, Maryland 20850.

A copy of this letter has been sent to the Detroit District Office, 300 River Place, Suite 5900, Detroit, MI 48307. Please send a copy of your response to that office.

If you have any questions, please contact Doreen Kezer, (240) 276-0125; doreen.kezer@fda.hhs.gov.

Sincerely yours,


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