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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

SEP 4 2007

William D. Tobler, MD
Mayfield Clinic & Spine Institute
2123 Auburn Avenue, Suite 441
Cincinnati, OH 45219

Dear Dr. Tobler:

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 May 8 through May 22, 2007, by an investigator from the FDA Cincinnati District Office. The purpose of this inspection was to determine whether activities and procedures related to your participation in the study titled [redacted] under IDE [redacted] sponsored by [redacted] complied with applicable federal regulations. The [redacted] used for this study is a device 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 discusses your written response to the observations noted at the time of the inspection, which was undated but was received by the Cincinnati District Office on August 22, 2007, and requests that you promptly implement corrective actions.

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 812 - Investigational Device Exemptions, and Part 50 - Protection of Human Subjects. At the close of the inspection, the FDA investigator presented a form FDA 483 - "Inspectional Observations" for your review, and discussed the observations listed on the form with you. The deviations noted on the FDA 483, your written response, and our subsequent review of the inspection report are discussed below:

- 1. Failure to ensure an investigation is conducted in accordance with the signed agreement with the sponsor, the investigational plan, applicable FDA regulations, and any conditions of approval imposed by FDA or the IRB [21 CFR 812.100, 21 CFR 812.110(b)].**

You failed to adhere to the above-stated regulations. Examples of this failure include but are not limited to the following:

- a.) There was no documentation in any of the records for the [] study subjects enrolled at your site to indicate that you evaluated their eligibility for the study prior to their enrollment. Specifically, the subject eligibility worksheets for the study and the Eligibility Case Report Forms (CRFs) require the signature and date of the investigator. None of the subject eligibility worksheets were signed by you, and you signed all [] Eligibility CRFs on 4/26/06, which was over two years after each subject was enrolled.

- b.) All of the CRFs for the study were signed in the space marked “Investigator’s Signature” by your study coordinator, and were dated “4/26/06” or later, even though the information on the CRFs was collected as early as 2003. There is no documentation to show that you reviewed or verified any of the information reported to the study sponsor on the CRFs. In addition, the study protocol requires that []
[]
[] You did not delegate your study coordinator to sign CRFs for you until 7/31/06, which was 2 days before the study was completed and closed.

- c.) Follow-up study visit evaluations were not performed for several subjects. For example:
 - i. Subject []: the []-month follow-up visit was performed by telephone on 4/[]/04. The study protocol does not allow for telephone follow-up visits, since that visit requires [] of the subject. In addition, the Pain Visual Analog Scale and Owestry Pain and Function Questionnaire to be completed by the study subject, which provided the primary efficacy data for the study, were completed by the study coordinator. The protocol requires study subjects to []
[]

 - ii. Subject []: the subject did not complete the Pain Visual Analog Scale and Owestry Pain and Function Questionnaire at the []-month visit on 10/[]/04, and the []
[] and [] were not performed at the []-month visit on 4/[]/04.

 - iii. Subject []: at the []-month visit on 5/[]/04 and at the []-month visit on 1/[]/06, the subject did not complete the Pain Visual Analog Scale and Owestry Pain and Function Questionnaire, and the follow-up [] evaluations were not performed. At the []-month visit on 12/[]/05, [] and [] evaluations were not performed.

 - iv. Subject []: at the []-month visit on 11/[]/04 and at the []-month visit on 6/[]/05, the [] and [] evaluations and examinations were not performed.

- d.) You allowed Institutional Review Board (IRB) approval to expire 3 times during the study. Specifically:
- i. The IRB initially approved the study for a period from 5/6/03 through 5/6/04. You did not submit a renewal request or obtain IRB approval to continue the study until 7/12/04. During the time the IRB approval had lapsed, you enrolled and/or performed study surgery on at least two subjects:
 - Subject [] was enrolled into the study on 3/[]/04 and had the study surgery on 7/2/04.
 - Subject [] was enrolled into the study on 5/[]/4 and had the study surgery on 5/[]/04.
 - ii. The IRB renewal expired again on 5/31/05. You did not submit a renewal request or obtain IRB approval to continue the study until 12/22/05. During the time IRB approval had lapsed, you performed study procedures and follow-up visits for several enrolled subjects.
 - iii. The IRB renewal expired again on 5/31/06. On 9/11/06, you submitted an annual progress report, which notified the IRB that the study was closed and completed on 8/2/06. On 2/19/07, you submitted a Study Closure Report/Final Report to the IRB stating that the study was closed on 8/4/06.
- e.) The initial IRB approval notice, dated 5/8/03, stated, “You are required to immediately report any adverse reaction or complications to the Institutional Review Board.” Your study records contain 14 reports of adverse events that were reported to the IRB on 9/6/06, which was after the study was closed. These events occurred from 11/[]/03 through 12/[]/05.
- f.) The study protocol requires that all “Intercurrent Events” (adverse events), device-related or not, be reported to the study sponsor on the appropriate CRF. At least four adverse events that were not reported to the study sponsor and/or the IRB were observed in subjects’ records. Specifically:
- i. Subject []: reported new-onset of restless leg syndrome, requiring medical treatment, at the []-month follow-up visit on 11/12/03.
 - ii. Subject [] reported new-onset of constipation, requiring medical treatment, at the [] month follow-up visit on 10/15/03.
 - iii. Subject []: reported significant increase in [] at the []-month follow-up visit on 2/[]/04, and again at the []-month follow-up visit on 4/[]/04.
 - iv. Subject []: the study records for the []-month visit on 2/[]/04 note the [] since [] [] or [] is listed as an anticipated adverse event in the study protocol.

2. Failure to maintain accurate and complete records for each subject's case history and exposure to the device [21 CFR 812.140(a)(3)].

a.) The study subjects' records contained numerous inaccuracies and inconsistencies. For example:

- i. Subject []: The []-month visit was not performed due to the subject's plans to be out of the country at the time. The subject was provided with the Pain Visual Analog Scale and Oswestry Pain and Function Questionnaire forms with instructions to complete and mail them to the study site in September 2004. The forms completed by the subject are dated 11/2/04. The study coordinator inaccurately transcribed the information onto CRFs, changing some of the subject's answers.
- ii. Subject []: At the []-month visit, performed on 2/[]/04, the [] evaluation indicated that the [] had [] since []. At the [] month visit, performed on 4/[]/04, the office visit note states [] and [] are in good position." The Case Report Form (CRF) notes the device is "intact." However, a Data Resolution Form initiated by the study sponsor on 4/20/05, questions whether the [] seen at the []-month visit was still present at the [] month visit, and your response was that the CRF should read, [].
- iii. Subject []: there are inconsistencies in the [] evaluation between the source record and the CRF at the pre-op visit on 11/[]/03.
- iv. Subject []: there are inconsistencies in the [] evaluation between the source record and the CRF at the pre-op visit on 3/[]/04.

b.) You failed to ensure that the current, IRB-approved version of the informed consent was correctly documented when executed by each of the subjects enrolled. Specifically, the initial IRB approval notice for the study, dated 5/8/03, required a revision to the consent form. The notice also stated that, when the modified consent form was submitted to the IRB for review, it "should carry the date of 05/06/03." The revised consent form was subsequently approved by the IRB on 6/12/03. However, none of the informed consent forms signed by the [] study subjects enrolled into the study contain any version date or confirmation that it is the correct form approved by the IRB.

In your written response to the deficiencies noted on the form FDA 483, you stated that you plan to implement several corrective actions, including installing a Department of Clinical Trials with a seasoned study coordinator as the department head, educating office staff on the definition of Serious Adverse Events, appropriately delegating authority, ensuring that all IRB approvals will be completed and submitted on time, and training of study coordinators to ensure documentation and reporting of protocol deviations. You also stated that you plan to use the FDA's guidance document regarding "Supervisory Responsibilities of Investigators" once it is "officially released by the FDA" for site staff training purposes. Your response is not adequate. Ultimate responsibility for accurate and complete implementation of the study protocols should lie with the investigator, rather than study coordinators and office staff. Your plan to use FDA's guidance document once it is released in the future is not adequate to ensure immediate compliance for this

and future studies.

Your general responsibilities as a clinical investigator include ensuring that an investigation is conducted according to the Clinical Study Agreement (which you signed on 1/31/03), the investigational plan, and applicable FDA regulations, for protecting the rights, safety, and welfare of subjects under the investigator's care, and for the control of devices under investigation. As a Clinical Investigator, you may delegate study tasks to other qualified personnel, but you may not delegate your responsibility to ensure that all study tasks are correctly performed. You failed to supervise the study so as to ensure that your general responsibilities as a clinical investigator were fulfilled.

Please provide us with documentation of a corrective action plan that addresses each of the violations noted above, such as a written procedure for ensuring study protocol compliance, written verification of training of study staff on study procedures and requirements, and/or internal study reviews or audits to ensure that such protocol violations have not occurred with other subjects and/or other studies, and that corrective actions have been implemented to prevent recurrence of the problems for future studies. Please provide us with a plan for future studies that will ensure you can adequately supervise study personnel and procedures that are performed at this site.

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 clinical 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 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. 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.

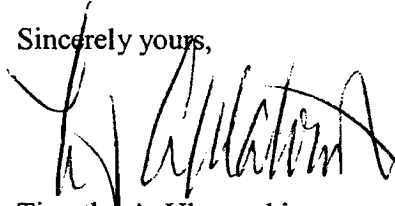
You will find information to assist you in understanding your responsibilities and planning your corrective actions in the FDA Information Sheets Guidance for Institutional Review Boards and Clinical Investigators, which can be found at <http://www.fda.gov/oc/ohrt/irbs/>. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. 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 Blvd., Rockville, Maryland 20850
Attention: Ms. Doreen Kezer, MSN, Chief, Special Investigations Branch.

A copy of this letter has been sent to the FDA Cincinnati District Office, 6751 Steger Drive, Cincinnati, OH 45237-3097. Please send a copy of your response to that office.

If you have any questions, please contact Ms. Doreen Kezer, MSN, at 240-276-0125 or at Doreen.Kezer@fda.hhs.gov.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Timothy A. Ulatowski". The signature is fluid and cursive, with a large initial "T" and "U".

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