

**WARNING LETTER**

VIA FEDERAL EXPRESS

Mark Adams, M.D.
5400 Mackinaw Road
Suite 2300
Saginaw, MI 48604-9515

OCT 23 2008

Dear Dr. Adams:

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 October 11 to October 18, 2007, by an investigator from the FDA Detroit District Office. The purpose of this inspection was to determine whether activities and procedures related to your participation in the clinical study, A Prospective, Multicenter, Controlled Clinical Trial of an Artificial Cervical Disc-LP at Two Levels for Symptomatic Cervical Disc Disease, IDE _____ complied with applicable federal regulations. PRESTIGE® LP Cervical Disc System 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 requests prompt corrective action to address the violations cited.

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, Part 50 -- Protection of Human Subjects, and Section 520(g) (21 U.S.C. 360j(g)) of 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 FDA 483 and our subsequent review of the inspection report are discussed below:

- 1) Failure to ensure that informed consent was obtained in accordance with 21 CFR Part 50; Failure to appropriately document informed consent [21 CFR 812.100; 21 CFR 50.27(a); 21 CFR 812.140(a)(3)].**

An investigator is responsible for ensuring that legally effective informed consent is obtained before a subject participates in any investigation. (21 CFR 50.20). That informed consent must be documented in writing using the Institutional Review Board (IRB) approved version of the informed consent form (ICF), signed and dated by the subject. (21 CFR 50.27(a).) You are required to keep accurate, current, and complete records of informed consent. (21 CFR 812.140(a)(3).) You failed to adhere to the above stated regulations. Examples of this failure include, but are not limited to, the following:

There is no documentation that Subject _____ signed the appropriate, IRB-approved informed consent prior to any study related procedures. Certain of your site records state that on 5/10/2007, subject _____ was screened and consented using an outdated ICF, and claim that the correct version of the ICF was signed by the subject on 6/5/2007. On 6/15/2007, on the basis of an informed consent form faxed to the sponsor, subject _____ was enrolled in the study, and the subject was taken to surgery under the protocol on _____. However, a letter dated 7/26/2007, from the sponsor, notifying the FDA, states that during an interim monitoring visit it was discovered that on the original ICF for subject _____ the subject signature dated 6/5/2007, which was faxed to the sponsor on 6/15/2007, was a photocopied signature that had been taped to that form.

2) Failure to report use of a device without obtaining informed consent to the sponsor and the reviewing IRB within five working days [21CFR 812.150(a)(5)].

If an investigator uses a device without obtaining informed consent, the investigator shall report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.

As noted above, Subject _____ did not have a signed informed consent documented prior to any study related procedures. Therefore, the device was placed on without informed consent and the IRB and sponsor should have been notified by 7/20/2007. The sponsor discovered this deviation on 7/23/2007 during a monitoring visit and subsequently you sent a letter to the IRB, dated 8/6/2007 informing them of this deviation.

3) 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 and 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. The exclusion criteria for this study states that a subject is to be excluded from the study if the subject is involved with current or pending litigation regarding a spinal condition. Subject _____ sent you a letter on 12/14/2006, and you

were issued a subpoena for medical records on _____, both documents concern a work-related injury for this Subject with a subsequent lawsuit against his employer concerning a spinal condition. There was no documentation of a resolution of this legal matter; however, the subject was enrolled in the study on 6/5/2007.

- b. Study related tests were not always performed as required by the investigational plan:
 - i. Subject _____ did not have any of the preoperative x-rays and the flexion/extension x-rays at the _____ week visit.
 - ii. Subjects _____ and _____ did not have any of the preoperative x-rays.
 - iii. Subject _____ did not have the preoperative flexion/extension x-rays. Therefore, half of the _____ subjects enrolled in this study did not have complete baseline tests.
 - iv. Subject _____ did not have flexion/extension x-rays at the _____ week visit.
- c. Follow-up visits were performed outside of the protocol window requirements:
 - i. Subject _____ -month and _____-month visits were _____ and _____ days late, respectively.
 - ii. Subject _____ month visit was _____ days late.
 - iii. Subject _____ month visit was _____ days late.
 - iv. Subject _____ month visit was _____ days late.
- d. The Investigator Agreement states that the investigator will provide the sponsor with a data set on each patient participant. It further defines the data set as all case report forms (CRFs) included in the investigational plan. The investigational plan states CRFs should be submitted to the sponsor within weeks of the visit. A 7/20/2007 letter from the sponsor states that you have submitted none of the expected _____ completed data sets for your _____ subjects.

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

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

- a. Source documents for Subject _____ are missing for the _____ week visit on 8/30/2007.
- b. Source documents for Subject _____ are missing for the questionnaires and physician's evaluation forms.

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.

Your general responsibilities as a clinical investigator include ensuring that an investigation is conducted according to the signed agreement, the investigational plan, applicable FDA regulations, and conditions of IRB approval. As an investigator you may delegate tasks to

other qualified staff, but you must supervise them to ensure that all applicable requirements are satisfied. You remain ultimately responsible for the conduct of the investigation, the maintenance of the records, and submission of reports in accordance with the applicable regulations, the investigational plan, and local policy.

In addition to specific issues identified above, there is a discrepancy in device accountability records for your site. The sponsor's printout dated 10/10/2007, states there are subjects who received the investigational device at your site. Your device accountability log states only subject received an investigational device. Please clarify this with the sponsor and address this issue in your response.

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. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. 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.

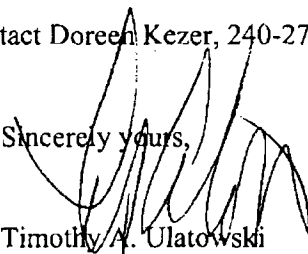
You will find information to assist you in understanding your responsibilities and planning your corrective actions in the FDA Information Sheets Guidance for Institutional Review Boards and Clinical Investigators, which can be found at <http://www.fda.gov/oc/ohrt/irbs/>. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. Send your response to:

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, Chief, Special Investigations Branch.

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

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

Sincerely yours,



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