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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Blvd.
Rockville MD 20850

OCT 1 2007

WARNING LETTER

VIA FEDERAL EXPRESS

Michael Bradford, M.D.
Nevada Orthopedic & Spine Center
2650 N. Tenaya Way, 3rd Floor, Suite 301
Las Vegas, Nevada 89128

Dear Dr. Bradford:

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 February 16 to March 20, 2007, by an investigator from the FDA San Francisco District Office. The purpose of this inspection was to determine whether activities and procedures related to your participation in the clinical study of the [redacted], sponsored by [redacted], in support of PMA #[redacted], complied with applicable federal regulations. [redacted] 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). In addition, this letter discusses your written response to the noted violations, dated April 17, 2007, postmarked June 20, 2007, and received in the FDA San Francisco District Office on July 9, 2007 and also requests prompt corrective action to address the 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, 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 Ms. Heather Little-Tierney, your study coordinator.

Your response letter addresses each of the FDA 483 items and in most cases states that no further action is required. You do not describe what, if any specific steps have been implemented to correct the violations or prevent future occurrences, or how they will prevent future deviations. In general, your letter indicates a lack of understanding of the regulatory

requirements that clinical investigators must meet, and it includes few corrective actions taken or planned, with regard to the deviations noted during the inspection. It is important for a clinical investigator to understand that unless the physical safety of a subject demands otherwise, treatment of study subjects must adhere to the requirements of the investigational plan. The completion of study enrollment does not conclude your responsibility to comply with the signed agreement, investigational plan, and applicable FDA regulations for the study in question. In addition, if you intend to participate in other FDA-regulated clinical investigations of devices, that participation will be subject to the same regulatory framework, and so FDA would like to know what corrective actions you will undertake to prevent similar violations from recurring in the future. The deviations noted on the FDA 483 and our subsequent review of the inspection report are discussed below:

1. **Failure to obtain informed consent in accordance with the regulations regarding the protection of human subjects. [21 CFR 812.100 and 50.20]**

   Pursuant to 21 CFR 812.100, an investigator must ensure that informed consent is obtained in accordance with part 50. Pursuant to 21 CFR 50.20, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject. Examples of your failure to adhere to the above stated regulation include but are not limited to the following:

   All subjects were screened, randomized into the study, and assigned study case numbers prior to granting informed consent. In addition, nine subjects (Subjects # [redacted] and [redacted]) were screened, randomized into the study, and assigned study case numbers, although they never consented to participate in the study and did not participate in subsequent study activities.

   In response to this violation, Ms. Little-Tierney told the FDA investigator that she informed all prospective study subjects of their randomization to either the control arm or the experimental arm while she was going through the process of obtaining their informed consent. The protocol specifically states, "No case will be enrolled without [redacted] Informed Consent [redacted]"

2. **Failure to ensure that an investigation is conducted according to the signed agreement, investigational plan, and applicable FDA regulations [21 CFR 812.100 and 812.110(b)**.

   Pursuant to 21 CFR 812.100 and 812.110(b), an investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, investigational plan and applicable FDA regulations. You failed to adhere to the above-stated regulations. Examples of this failure include but are not limited to the following:

   a.) Three subjects were enrolled who failed to meet study eligibility criteria. Specifically Subjects # [redacted], and [redacted] each had a [redacted] prior to beir

screened for the study. According to the protocol, [redacted]. [redacted] are to be excluded from the study.

b.) According to the protocol, [redacted]. Approximately 23 percent of all study visits ([redacted] visits) were outside the acceptable windows. Examples include but are not limited to the following:

- The date of [redacted] for Subject #[redacted] was November [redacted], 2003, and the [redacted] visit occurred on January [redacted], 2004.
- The date of [redacted] for Subject #[redacted] was November [redacted], 2003, and the [redacted] visit occurred on March [redacted], 2005.
- The date of [redacted] for Subject #[redacted] was September [redacted], 2003, and the [redacted] visit occurred on May [redacted] 2006.

3. 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 regulation. Examples of this failure include but are not limited to the following:

a.) The protocol states that [redacted]' and that [redacted] At least three subjects had documentation in their medical records of complications that were not reported to the study sponsor. Specifically:

- For Subject #[redacted], the medical records for the [redacted] visit indicate that the subject developed [redacted], but the Physical Exam case report form indicates there were no complications.
- For Subject #[redacted], the medical records for the [redacted] visit document pain in [redacted] but the Physical Exam case report form indicates there were no complications.
- Subject #[redacted] experienced [redacted] and examination revealed [redacted] at the [redacted] visit. However, the Physical Exam case report form lists no complications.

b.) The Screening case report forms for Subjects #[redacted], and [redacted] indicate that these subjects have no pre-existing [redacted], but, as noted above in citation **2a**, the medical records for these subjects have multiple entries regarding history of [redacted].

c.) No records were found to verify that any enrolled subjects were eligible to participate in the study based on the results of the [redacted] evaluation. According to the protocol, subjects can be included in the study only if they have a [redacted]

d.) All worksheets used to screen the subjects (original source documents) were discarded after the information was transcribed to case report form [redacted]. In addition, the sponsor's screening list indicates that [redacted] subjects were screened at your clinical site, but Ms. Little-Tierney was only able to find completed screening records for [redacted] subjects.

e.) [redacted] evaluations (two views) were not available for review by the FDA investigator for Subjects # [redacted] and [redacted]

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. 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/.

We also note that according to Ms. Little-Tierney, all of the original medical records involved in this study were discarded after they were scanned. Your response to the FDA 483 indicates that your medical practice normally operates as a [redacted] office, relying on [redacted] copies of records. Any [redacted] records you maintain must be sufficient to meet your underlying recordkeeping obligations. As we noted above, as an investigator, you are required to maintain accurate, complete, and current records as provided for in 21 CFR 812.140 (a). You must maintain all required records for a period of two years after the latter of the following two dates: the date on which the investigation is terminated or completed, or the date that the records were no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol. (See 21 CFR 812. 140(d)). For additional information regarding your obligations when using electronic records in FDA-regulated clinical investigations, please see FDA's Guidance for Industry, Computerized Systems Used in Clinical Investigations, available at http://www.fda.gov/cder/guidance/7359fnl.pdf.

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
9200 Corporate Boulevard, HFZ-310
Rockville, Maryland 20850
Attention: Linda Godfrey, Branch Chief.

A copy of this letter has been sent to the FDA San Francisco District Office, 1431 Harbor Bay Parkway, Alameda, CA 94502. Please send a copy of your response to that office.

If you have any questions, please contact Ms. Linda Godfrey at (240) 276-0125 or by email at Linda.Godfrey@fda.hhs.gov.

Sincerely yours,

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

IRB/Purged Copy to:

Sponsor/Purged Copy to: