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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

MAY - 6 2008

WARNING LETTER

VIA FEDERAL EXPRESS

Merrill W. Reuter, M.D., Ph.D.
Advanced Orthopaedics of South Florida
7625 Lake Worth Road
Lake Worth, Florida 33467-2534

Dear Dr. Reuter:

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 December 13, 2007 to December 21, 2007 by an investigator from the FDA Florida District Office. The purpose of this inspection was to determine whether your activities as both sponsor and investigator in the [redacted] designated herein as the [redacted] and [redacted] designated herein as [redacted] complied with applicable federal regulations. 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 dated January 30, 2008 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, 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 Form FDA 483, your written response, and our subsequent review of the inspection report are discussed below:

Failure to ensure proper monitoring of the investigation, obtain IRB review and approval, submit an IDE application to FDA, receive FDA approval of the IDE before beginning the investigation, and control devices under investigation [21 CFR 812.100, 21 CFR 812.110(a), 21 CFR 812.40 and 21 CFR 812.42].

You acted as both sponsor and clinical investigator in the and the As a sponsor, you are required to obtain a new IDE if a significant risk device that is approved for one indication is intended to be used in a clinical study for a new indication. The devices under investigation are significant risk devices as defined by 21 CFR 812.3(m). They are cleared by FDA to They were used in these studies as as stated in your protocols. Before beginning investigations of these devices for these new indications, you were required, as sponsor, to submit IDE applications and obtain FDA-approved IDEs. 21 CFR 812.20(a), 21 CFR 812.40, and 21 CFR 812.42. In addition, as a sponsor, you are responsible for ensuring proper monitoring of the investigations and ensuring that IRB review and approval are obtained. 21 CFR 812.40 and 21 CFR 812.42.

As a clinical investigator, you are responsible for ensuring that an investigation is conducted according to applicable FDA regulations, ensuring that IRB and FDA approval are obtained before allowing any subjects to participate, ensuring that informed consent is obtained in accordance with 21 CFR Part 50, and controlling devices under investigation. 21 CFR 812.100 and 21 CFR 812.110(a).

Examples of your failure to adhere to these regulations include, but are not limited to, the following:

1. You conducted the and without obtaining IRB and FDA approval.

2. Regarding the you failed to obtain an FDA-approved investigational device exemption (IDE) prior to conducting this study in 2002. You which is FDA-cleared to of the following subjects in 2002:

3. Regarding the you failed to obtain an FDA-approved IDE prior to conducting this study in 2005. You implanted a which is FDA-cleared to of the following subjects in 2005:

4. There is no documentation that the device studies were monitored in 2002 and 2005.

5. There are no device accountability records to show which investigational device was used in which subject for [redacted] device studies.

Your written response states that prior to this work on the [redacted] device studies, all of the research performed by your office had been done with corporate sponsors who prepared IDE applications and helped you stay on track record-wise. Your response acknowledges that you failed to obtain FDA approval before initiating both studies and that you failed to obtain IRB approval before initiating the [redacted] You contend that you did obtain IRB approval before initiating the [redacted] but that you cannot to date locate documentary proof of such approval. Your response also acknowledges that, for both studies, you were negligent in your recordkeeping, monitoring, and device accountability. Your response states that you take full responsibility for your breach of FDA protocol in conducting the [redacted] studies and that with any future studies undertaken you will contact the FDA to ensure that you submit all required forms and documentation. Your response also states you will know what is required of you and will do it, including adopting the responsibilities of the sponsor if applicable, and you will know the responsibility of the IRB.

Your response is inadequate in that contacting the FDA may be a first step; however, you need a corrective action plan that includes training, as you are responsible for knowing and following the regulations pertinent to your activities as a sponsor/investigator in FDA-regulated studies. Please provide copies of policies, procedures, and training with expected completion dates that are being developed and implemented to prevent the recurrence of these violations in future clinical studies.

Failure to ensure that informed consent is obtained in accordance with 21 CFR Part 50 [21 CFR 50.27(a) and 21 CFR 812.100].

Although you had written consent forms for the [redacted] studies and most subjects signed them, the forms were not IRB-approved. In addition, subject [redacted] or the subject's legally authorized representative did not sign and date the written informed consent form prior [redacted] of the investigational device on [redacted] Therefore, you did not obtain valid informed consent for all [redacted] subjects enrolled in the [redacted] studies.

Your written response states you will ensure that the nurses who erroneously signed the consent form as witnesses of verbal consent will have a complete understanding of all FDA regulations regarding the signing of written informed consent forms. As an investigator, you are ultimately responsible for ensuring that no subject is involved in research unless legally effective informed consent is obtained. Also, while it is important that your nurses understand how to properly document informed consent, obtaining the subject's signature is only one part of the consent process. You and your staff should be aware of the entire informed consent process. Your response is also inadequate in that you did not describe a corrective and preventive action plan. Please provide copies of

procedures and training with expected completion dates that are being developed and implemented to prevent the recurrence of these violations in future clinical studies.

Your written response references Form FDA 1572 "Statement of Investigator." Please note that Form 1572 is used for clinical trials involving FDA-regulated drugs and biologics. For device studies, a sponsor shall obtain a signed investigator agreement from all clinical investigators participating in the study. 21 CFR 812.43(c).

Your written response states that the [redacted] CEO, in consultation with the medical executive board, authorized the [redacted] and that an IRB approved the [redacted] You stated that you relied on the medical board and the IRB to alert you to your responsibilities and to ensure that proper procedures were followed. You also stated that because of your lack of understanding in getting proper IRB approval, you failed to maintain documentation of IRB correspondence and to prepare and submit reports (unanticipated adverse device effects and progress) to the IRB. The regulations in 21 CFR Part 812 describe sponsor responsibilities as well as those of investigators. IRB responsibilities are spelled out in 21 CFR Part 56, Institutional Review Boards. These three sets of responsibilities overlap to ensure appropriate conduct of clinical studies and the protection of the rights and welfare of participating subjects. Therefore, though the IRB involved in your study may have been remiss in fulfilling its responsibilities, you are still held responsible for knowing and following the regulations pertinent to your activities as a sponsor/investigator in FDA-regulated studies.

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 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, MSN, Food and Drug Administration, Center for Devices and

Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, 9200 Corporate Boulevard, HFZ-311, Rockville, Maryland 20850.

A copy of this letter has been sent to the Florida District Office, 555 Winderley Place, Suite 200, Maitland, FL 32751. Please send a copy of your response to that office.

If you have any questions, please contact Ms. Doreen Kezer by telephone at (240) 276-0125 or via e-mail at doreen.kezer@fda.hhs.gov.

Sincerely yours,

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