

Food and Drug Administration
Center of Devices and
Radiological Health
2098 Gaither Road
Rockville, Maryland 20850

JUL 14 2006

WARNING LETTER

VIA FEDERAL EXPRESS

William J. Bose, M.D.
The Orthopedic Group
6144 Airport Blvd.
Mobil, AL 36604

Dear Dr. Bose:

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 March 13 through April 12, 2006, by an investigator from the FDA New Orleans District Office. The purpose of this inspection was to determine whether activities and procedures related to your participation in the clinical study, *A Non-randomized, Safety and Efficacy Study of the [REDACTED] An FDA Investigational Study*, [REDACTED] sponsored by [REDACTED] complied with applicable federal regulations. The [REDACTED] 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 and discusses your written response dated May 15, 2006, 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 C.F.R.) Part 812 - Investigational Device Exemptions and Part 50 - Protections of Human Subjects. 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, and our subsequent review of the inspection report and your written response are discussed below.

In your response, you acknowledge that at the onset of the study you were unfamiliar with the requirements and complexity of documentation for an IDE clinical study and that your study coordinator was also inexperienced and not trained to these requirements. You acknowledge your role and responsibilities as a clinical investigator and state you will work diligently with the FDA, the reviewing IRBs, and the sponsor to ensure that all observations made by the FDA have been fully addressed and that all future activities comply with the applicable regulations. You have taken steps to correct some of the violations noted, however, your corrective action plan does not fully address all the noted violations. You and your coordinator may consider seeking training specific to medical device good clinical practice (GCP).

Failure to ensure an investigation is conducted in accordance with the signed agreement, the investigational plan, and applicable FDA regulations. [21 CFR 812.100 and 21 CFR 812.110(b)]

1. You failed to maintain documentation of correspondence with the two reviewing local IRBs [REDACTED] for reporting of adverse events/complications in accordance with the investigational plan and IRB policy. Examples of this failure include, but are not limited to the following:
 - A) Subject [REDACTED] was hospitalized for cellulitis. The subject received intravenous (IV) and oral (PO) antibiotics for three weeks in December 2003. There is no documentation that the IRB was informed of this event and hospitalization.
 - B) Subject # [REDACTED] became pregnant during the study and could not have X-Rays performed in accordance with the investigational plan, however there is no documentation the pregnancy or deviation from the investigational plan was reported to the IRB.
 - C) Subject # [REDACTED] developed an abscess around the implanted device that required removal of the device. There is no documentation that the IRB was informed of the event and that the investigational device was removed.

In your response, you acknowledge that documentation of correspondence with the IRBs was not accurately maintained. You state that in the future all IRB correspondence, submission, approvals, and reviews will be maintained in the regulatory binder. Doing this should assist you in the maintenance of correspondence documentation. Your response is incomplete in that it did not address ensuring all correspondence/reporting is performed in accordance with the investigational plan, IRB policy, and Federal Regulations. Please provide copies of policies, procedures, and training with expected completion dates that are being developed and implemented to ensure correspondence with the IRB, the sponsor, and regulatory agencies is performed as required.

2. Subjects were enrolled that did not meet the eligibility criteria. Examples of this failure include but are not limited to the following:

- Subject [REDACTED] and subject [REDACTED] have documented diagnoses of morbid obesity (according to the diagnoses listed in their medical history), however, morbid obesity is an exclusion criteria as dictated by study protocol.

In your response, you state morbid obesity was not specifically defined by using a specific body mass index (BMI) to allow investigator discretion. Based on general condition, age, and activity level of these subjects, you viewed these subjects as appropriate candidates. You did not understand that you should have noted this in the study records. Please note that because the protocol specifies that morbid obesity is an exclusion criteria, enrollment of these subjects is considered a protocol deviation and should have been documented as such. If specifications in a protocol are incorrect, an amendment should be submitted to the reviewing IRB to provide for the flexibility that you describe. Please provide the corrective and preventive actions you have taken or will take to address this type of situation in the future.

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

An investigator is responsible for ensuring that the Institutional Review Board (IRB) approved version of the informed consent document is obtained from each subject participating in the investigation prior to performance of any study-related procedures. You failed to adhere to the above stated regulations. Examples of this failure include but are not limited to the following:

- Subject [REDACTED] had the investigational device implanted on January 12, 2004, however, the consent was not signed until February 9, 2004.

In your response, you state your research team was unable to locate the original consent document, but subject [REDACTED] was consented. You acknowledge that your coordinator "backdated" the consent document for subject [REDACTED]. You are adding a note to the file to clarify this issue.

The regulations mandate that a subject must date and sign the informed consent document prior to any study related procedure. Your response is incomplete in that it did not include policies and/or procedures to ensure all subjects are consented prior to any study related procedures and that these records are maintained. Please provide copies of policies, procedures, and training with expected completion dates that are being developed and implemented to ensure informed consent is obtained and documented prior to any study related procedures. In addition, please clarify what actions are being taken to ensure the documentation of the informed consent is maintained throughout the study.

Failure to maintain accurate, complete, and current case histories. [21 CFR 812.140(a)(3)]

You failed to maintain accurate, complete, and current records of each subject's case history and exposure to the device, as required by 21 CFR 812.140(a)(3) and the study protocol. Examples of this failure include, but are not limited to the following:

1. Protocol inclusion #6 requires subjects to have a pre-operative Harris Hip Score (HHS) of less than 70 . Harris Hip Scores were not documented in 21 of 21 subjects' charts inspected by the FDA investigator.

In your response, you note you did not document the actual HHS for subjects prior to enrollment, but you evaluated each patient preoperatively and only patients who had a HHS of less than 70 were enrolled. You acknowledge that documentation of the inclusion-exclusion criteria should have been completed in the patient's medical history. You have developed and implemented the use of a source document to assist in the assessment and documentation of the HHS. Implementing this tool should assist you in your documentation of the HHS.

2. Discrepancies were observed between source records and case report form (CRF) entries. Examples include:
 - A) Subject [REDACTED] underwent right hip arthroscopy with resection of labral tear on January 6, 2004, however, this prior surgery was not documented on the May 17, 2004, pre operative CRF. The check box on the CRF asking if the subject has had prior surgery in the past 12 months was checked "no".
 - B) Subject's [REDACTED] and [REDACTED] have discrepancies in the documentation of the size of the implanted cup. The sizes noted on the CRFs and on the operative reports differ.

| Subject | CRF – Implanted Cup Size | CRF – Femoral Implant Size | Operative Report- Cup Size |
|------------|--------------------------|----------------------------|--|
| [REDACTED] | 50 | 44 | 52 (2 nd Op report noted a size 50) |
| [REDACTED] | 54 | 48 | 56 |

In your response, you state in order to ensure that all discrepancies have been identified and corrected, the sponsor has agreed to send a monitor to your site to review all the patients' charts and to identify any discrepancies or issues. This should assist you in clarification of data discrepancies. Documentation of all protocol related elements is a critical component to conducting clinical trials including, diagnostic procedures, adverse events, and communications with the subjects. This often requires documentation in addition to what is required in your everyday practice.

Failure to submit progress reports on the investigation to the sponsor, the monitor, the reviewing Institutional Review Board (IRB) at regular intervals, but in no event less often than yearly. [21 CFR 812.150(a)(3)]

You failed to submit progress reports to the reviewing IRBs at regular intervals, but in no event less often than yearly. Examples of this failure include but are not limited to the following:

- A) [REDACTED] IRB initially reviewed and approved the study April 8, 2003, for one year. The continuing review was not submitted until April 22, 2004, and not approved until May 4, 2004.
- B) [REDACTED] initially reviewed and approved the study on March 28, 2003, for one year however, the continuing review was not submitted to the IRB until April 22, 2004, and approved on May 27, 2004.

In your response, you acknowledge that IRB progress reports were not submitted on an annual basis. In order to correct this issue, you are providing a report to each IRB detailing the events that occurred and will also create a note to the file. Your response is incomplete in that it does not address ensuring that IRB progress reports are submitted to reviewing IRB in accordance with the IRB policy and applicable regulations. Please provide policies, procedures, and training with expected completion dates that are being developed and implemented to ensure IRB approval/oversight are maintained.

Failure to maintain records of device receipt, use, and disposition. [21 CFR 812.140(a)(2)]

You failed to maintain device accountability records. Investigators are responsible for maintaining records of receipt, use, or disposition of a device that relate to the following: type and quantity of the device; dates of its receipt; batch number or code mark; names of all persons who received, used, or disposed of each device; and why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of.

- There were no device accountability records to show receipt, use/implantation, and disposition/return to the sponsor of investigational devices.

You noted in your discussion with the FDA investigator the sales representative brought the devices directly to the operating room prior to their implantation. It is an investigator's responsibility to maintain records of an investigational device receipt, use, and disposition.

In your response, you state you are retrieving device accountability records and are completing an investigational device log. Proper completion of a device accountability log should assist you to track devices with this trial and future trials.

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.

During the inspection you discussed with the FDA investigator that you believe some of the observations on the Form FDA 483 were the responsibility of the sponsor, and that you trusted the sponsor was following all regulations. The regulations in 21 CFR Part 812 describe sponsor responsibilities for the conduct of investigational device studies as well as those of investigators. The regulations in 21 CFR Part 50 describe responsibilities of the investigator and IRB in the informed consent process and 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 sponsor and IRB involved in your study may have been remiss in fulfilling their responsibilities, you are still held responsible for knowing and following the regulations pertinent to your activities as a clinical investigator in FDA-regulated studies.

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 C.F.R. 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, 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 New Orleans District Office, 297 Plus Park Boulevard, Nashville, TN 37217. Please send a copy of your response to that office.

