



WARNING LETTER

VIA FEDERAL EXPRESS

Robert D. D'Ambrosia, M.D.
Professor and Chairman
Orthopaedics Administration
12631 East 17th Avenue, Room 4501
Aurora, CO 80045

APR 4 2008

Dear Dr. Ambrosia:

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 November 15 to December 6, 2007, by an investigator from the FDA Denver District Office. The purpose of this inspection was to determine whether activities and procedures related to your participation in the clinical study [redacted] [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). This letter also requests prompt corrective action to address the violations cited and discusses your December 20, 2007, written response 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 -- Protection 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, your written response, and our subsequent review of the inspection report are discussed below:

Failure to ensure investigational devices were used only with subjects under the investigator's supervision and that the investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations. [21 CFR 812.100 and 812.110(c)]

Investigators are responsible to ensure investigational devices are to be used only with subjects under their supervision. Although subjects were enrolled and treated at additional sites by sub-investigators you are the responsible investigator for this study. This includes subjects enrolled by sub-investigators [redacted] and [redacted]. You failed to supervise the conduct of the investigation and ensure the investigation and clinical work performed by sub-investigators was conducted according to the investigational plan, protocol, and signed investigator agreements.

Specifically, there is no documentation of oversight, training, or informing sub-investigators of their obligations for [redacted] and [redacted]. Such responsibilities are described in the Clinical Investigator Agreement and Protocol.

In your response you state you "view the audit as a learning opportunity from which [you] can educate [your]self and the faculty within the department to assure these types of errors do not happen in the future." You state you now understand that as a Principle Investigator (PI), you are "responsible for the actions of all the personnel involved in the study, including sub-investigators at remote sites." However, the purpose of this oversight is to ensure the 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 however, 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 and the investigational plan. Your response is inadequate in that you did not include a plan to ensure adequate oversight and conduct of the study. Please provide copies of policies and procedures, with expected completion dates, that are being developed and implemented to ensure adequate oversight and conduct of the investigation.

Failure to obtain proper informed consent prior to involving human beings as subjects. [21 CFR 50.20, 50.27(a), 812.100, and 812.140(a)(3)(i)]

An investigator is responsible for obtaining informed consent on the Institutional Review Board (IRB) approved version of the informed consent document from each subject participating in the investigation prior to involving them as subjects. You failed to ensure that informed consent was obtained from subjects in accordance with the federal regulations. Examples of this failure include but are not limited to the following:

A) Investigational devices were [redacted] in [redacted] subjects without obtaining informed consent:

Subject [redacted] was [redacted] with the device on August 15, 2003, Subject [redacted] was [redacted] on February 27, 2004, and Subject [redacted] was [redacted] on [redacted]

March 15, 2004, however you did not obtain informed consent for any of these subjects.

- B) An IRB approved version of the informed consent document was not used to obtain informed consent from each subject enrolled. Examples of this failure include but are not limited to the following:
- 1) [redacted] of [redacted] subjects enrolled at Dr. [redacted] site were not consented with the [redacted] Institutional Review Board [redacted] approved consent document; subjects [redacted]
 - 2) Subject [redacted] was enrolled and signed the informed consent document on February 23, 2004, however the consent document had expired January 8, 2004.
- C) Study related procedures were performed prior to obtaining informed consent. Examples of this failure include but are not limited to the following:
- 1) Subjects [redacted] and [redacted] had [redacted] visits, assessments, and [redacted] prior to obtaining written informed consent.
 - 2) Subject [redacted] had a [redacted] evaluation on October 9, 2003, and a [redacted] on November 25, 2003, however, written consent was not obtained until December 18, 2004, with a consent document that had expired on January 8, 2004.

In your response you state you are scheduled to participate in the Office for Human Research Protection's (OHRP) sponsored course on Human Subjects Protections in April 2008. This training is appropriate; however, you may also consider training related to Good Clinical Practice (GCP) and investigator responsibilities for you and your research assistant. In your response you have included copies of letters updating subjects on the status of the study and updated consent documents that are being sent to all study participants. Page two of the letter includes a misleading statement: [redacted] that you [redacted] as part of your study participation has been cleared for marketing in the United States by the FDA in a very similar form." This device has not been cleared by the FDA for marketing. Your response is inadequate in that your letter includes a misleading statement and you did not include a corrective plan to ensure that this violation does not occur in the future. Please provide copies of policies, procedures, and training with expected completion dates that are being developed and implemented to ensure informed consent is obtained with the most current IRB approved consent document prior to any study related procedures being performed. In addition, please remove the incorrect information from your update letter to subjects and provide an update of the status of informing all subjects enrolled in the study.

Failure to conduct the investigation according to the signed agreement, the investigational plan, and applicable FDA regulations. [21 CFR 812.100 and 21 CFR 812.110(b)]

An investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, 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.

A) Follow-up examinations and diagnostic tests were not performed in accordance with the investigational plan. Examples of this failure include but are not limited to the following:

- 1) Subject [redacted] was not performed. The [redacted] case report form (CRF) states "Not Done."
- 2) Subject [redacted] CRF is incomplete in that it notes the [redacted] "ND." The [redacted] year assessment CRFs notes "NS" for all assessments and [redacted]
- 3) Subject [redacted] Questionnaire for the [redacted] month, [redacted] month, and [redacted] year visits were not performed.

B) In accordance with the protocol's Inclusion Criteria the [redacted] Assessment must be [redacted] or greater. Subjects with [redacted] of less than [redacted] were enrolled. Examples of this failure include but are not limited to the following:

- 1) Subject [redacted] Inclusion/Exclusion CRF states the [redacted] Assessment is greater than [redacted] however, the [redacted] Assessment was documented on the [redacted] Evaluation CRF as [redacted] on June 4, 2003.
- 2) Subject [redacted] Inclusion/Exclusion CRF states the [redacted] Assessment is greater than [redacted] however, the [redacted] Assessment was not documented and the subject was enrolled on August 11, 2003.
- 3) Subject [redacted] Inclusion/Exclusion CRF states the [redacted] Assessment is greater than [redacted] however, the [redacted] Assessment was documented on the [redacted] Evaluation CRF as [redacted] on October 20, 2003.
- 4) Subject [redacted] Inclusion/Exclusion CRF states the [redacted] Assessment is greater than [redacted] however, the [redacted] Assessment was documented on the [redacted] Evaluation CRF as [redacted] on February 23, 2004.

Your response is inadequate in that it does not address ensuring that your investigations are conducted according to the signed agreement, the investigational plan and applicable FDA regulations. Please provide copies of policies, procedures, and training with expected completion dates that are being developed and implemented to ensure the study is conducted in accordance with the signed agreement, the investigational plan, and applicable FDA regulations. The investigation has been closed by the [redacted] Institutional Review Board [redacted] however, there are still subjects continuing to receive follow-up care. Please provide a copy of your plan to ensure subject's follow-up exams are performed, documented, and reported for all subjects enrolled.

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

An investigator is responsible for maintaining accurate, complete, and current records of each subject's case history and exposure to the device, which encompasses the case report forms (CRF) and supporting data. You failed to maintain accurate, complete, and current records of subjects' case histories as required by 21 CFR 812.140(a)(3). Examples of these failures include, but are not limited to the following:

- A) The [redacted] Summary CRF for subject [redacted] is dated February 27, 2004, however the [redacted] report notes it was performed on March 8, 2004.
- B) Subject [redacted] March 7, 2005, [redacted] Month [redacted] Summary CRF noted [redacted] results however, [redacted] was performed at that time. The progress report notes that [redacted] will be performed at the next visit.
- C) Subject [redacted] March 25, 2004, [redacted] CRF notes [redacted] however, the CRF complication box is checked [redacted] The subject later suffered a [redacted] which lead to the [redacted] becoming [redacted] and this required a revision of the [redacted] in September 2004.
- D) The medical history section of the protocol states any pre-existing disease or condition that may affect the results of the [redacted] must be documented. Subject [redacted] She is currently being treated with [redacted] and [redacted] for this condition. However, the Medical History and Medication CRFs do not note this diagnosis or these medications.

Your response is inadequate in that it does not address maintenance of accurate, complete, and current records of each subject's case history and exposure to the device, which encompasses the case report forms (CRF) and supporting data. Please provide copies of policies, procedures, and training that are being developed and implemented to ensure that documentation of case histories are accurate, complete, and current. Please include completion dates for this corrective action.

Failure to submit to the sponsor and the reviewing IRB reports of any unanticipated adverse device effects occurring during the investigation. [21 CFR 812.150(a)(1)]

An investigator is responsible for submitting to the sponsor and the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. You failed to document and report unanticipated adverse device effects to the IRB and sponsor. Examples of this failure include but are not limited to the following:

- A) Subject [redacted] March 25, 2004, [redacted] CRF notes [redacted] there is a note to file, dated August 17, 2007, stating the [redacted] caused the [redacted] to become [redacted] and this required a revision of the [redacted] in September 2004. This serious unanticipated adverse event was not reported to the [redacted] until November 11, 2004.

B) Subject [redacted] February 28, 2005. [redacted] of the [redacted] revealed [redacted] and other [redacted]. There is obvious instability of [redacted]. The Physician Progress Note states, [redacted]. The [redacted] and a revision of the [redacted] was performed on March 25, 2005. This serious unanticipated adverse event was not reported to the [redacted].

Your response is inadequate in that it does not address reporting of unanticipated adverse device effects. Please provide copies of policies, procedures, and training with expected completion dates that are being developed and implemented to ensure that unanticipated adverse device effects are documented and reported to the sponsor and reviewing IRB in accordance with the investigational plan and Federal Regulations.

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.

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 sponsor 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 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.

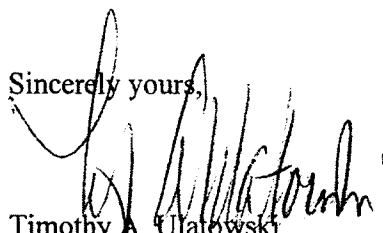
You will find information to assist you in understanding your responsibilities and planning your corrective actions in the FDA Information Sheets Guidance for Institutional Review Boards and Clinical Investigators, which can be found at <http://www.fda.gov/oc/ohrt/irbs/>. Any submitted corrective action 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-310, Rockville, Maryland 20850.

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A copy of this letter has been sent Denver District Office, 6th and Kipling Street, PO BOX 25087, Denver, CO, 80225-0087. Please send a copy of your response to that office.

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

Sincerely yours,



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

