

Food and Drug Administration
Center for Device and
Radiologic Health
9200 Corporate Boulevard
Rockville, Maryland 20850

WARNING LETTER

VIA FEDERAL EXPRESS

Thomas P. Gross M.D.
Midlands Orthopedic Group, LLC
1013 Lake Murray Blvd
Irmo, SC 29063

FEB 24 2006

Dear Dr. Gross,

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 June 21 through July 1, 2005, by an investigator from the FDA Atlanta 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. The [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 actions to address the violations cited and discusses your written response (dated August 11, 2005) 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) and Premarket Approval (PMA) applications 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, 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 is discussed below:



Protecting and Promoting Public Health

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)]

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

- You implanted seven subjects, [REDACTED]; which is an unapproved component for use in this study.

In your response, you state you were unaware that these components were not FDA approved for use as part of this IDE study and that it was an oversight. Your response is inadequate in that you did not supply a corrective action plan to ensure the investigation will be conducted in accordance with the signed agreement, 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 proper conduct of the investigation. In addition, provide documentation that these subjects were informed of receiving an unapproved medical device.

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 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:

- The [REDACTED] IRB notified you on February 15, 2001, "The consent form is also approved pending inclusion of the LMC cost and payment language..... The study may not begin until the corrected informed consent is received." You began the study without revising the language in the consent form and obtaining IRB approval of the consent. You obtained informed consent with the unapproved consent document for all 241 subjects enrolled at Lexington Hospital.

In your response, you state you have contacted the IRB to discuss this issue. In a letter dated July 26, 2005, the IRB states this language was no longer needed as part of the consent; however this is 4 years after you began the study, at which time the LCM cost and payment language was required. This response is inadequate, as you did not provide a corrective action plan to ensure informed consent is obtained prior to enrolling any subjects on an investigational study. Please provide copies of policies, procedures, and training with expected completion dates that are being developed and implemented to

ensure proper approval of informed consent documents is obtained prior to enrolling any subjects on a study. In addition, please provide dated documentation of when the informed consent document was approved by the IRB.

Failure to submit complete, accurate, and timely reports. [21 CFR 812.150(a)(3)]

An investigator shall submit progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly. You failed to adhere to this regulation. Examples of this failure include but are not limited to the following:

The [REDACTED] IRB requested "Quarterly update reports to be submitted to the IRB". There are discrepancies between dates of quarterly reports:

- A) On February 15, 2001, the IRB requested informed consent document changes prior to beginning the study.
- B) Your initial update is dated September 2, 2001, however the IRB approval letter is dated February 6, 2002.
- C) Your second update is dated November 1, 2001, and lists a previous report dated August 28, 2001. (Your first update was dated September 2, 2001).
- D) Your third update was prepared and signed three times (May 22, 2002, May 30, 2002, and August 9, 2002), however there is no documentation this was submitted to the IRB.
- E) Your fourth update states that the third update was submitted August 6, 2002.
- F) No documentation of updates since April 2005.

In your response, you note you gave the IRB verbal updates. Please provide the dated IRB meeting minutes documenting that the verbal quarterly reports were executed, reviewed, and accepted by the IRB. In addition, please provide policies and procedures you have developed to ensure IRB reports will be submitted and documented at required intervals.

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) Harris Hip Scores (HHS) were not documented in any of the 38 subjects' charts inspected.

In your response, you state you have not performed a total hip replacement on a patient who does not have a HHS of 70 or less, and that, while you do not formally calculate the HHS for the patients, you know the symptoms well enough to determine whether or not the score is less than 70. While this may be acceptable in your standard practice, clinical

investigations often require additional testing and documentation to evaluate a subject's eligibility status and the safety and effectiveness of the investigational device. Documentation of case histories is an essential component of conducting a clinical investigation; if it is not documented it is considered as not occurring. The investigational plan requires specific exams and diagnostic tests to be performed and the results documented at specified intervals throughout the study. Your response is inadequate, you did not supply a corrective action plan to ensure that the documentation of study-related data is performed accurately, completely, and in a timely manner. Please provide copies of policies, procedures, and training with expected completion dates that are being developed and implemented to ensure proper documentation of study data.

- 2) Femoral and acetabular component positions and migration were not documented on case report forms or maintained in source documents as required by the study protocol.

In your response, you state that you were not aware that you were expected to assess radiographs as you were collecting data throughout the course of the study. You expressed that you were under the impression that the measurements of the radiographs would be done during the analysis phase. You further stated you were notified by the sponsor, while the study was underway, that they had another method by which the radiographs would be measured and that you would not be responsible for the measurements. This change in your responsibilities and analysis techniques should be documented in the investigational plan. Please provide the documentation from the sponsor and IRB approval of this change in protocol.

- 3) Several inconsistencies and discrepancies were noted between Case Report Forms (CRFs) and source documents. FDA evaluates the accuracy and completeness of the data reported on the CRFs with the source documents to ensure its accuracy. Some examples are:
 - A) Subject [REDACTED] there are two 6-week CRFs---one is dated April 9, 2003, and the other is dated December 11, 2002. The assessment information on the CRFs is different on each form.
 - B) Subject [REDACTED] there are two 1-year follow-up CRFs---one is dated March 3, 2003, and the other February 14, 2003.

In your response, you state you conducted the study using the forms provided by the sponsor. As the sponsor changed its forms, you changed your methods for collecting data. In your response, you stated you made all corrections, however, due to limited resources, they were not made in a timely fashion. The above listed are just several examples of documentation errors. Therefore, you have not made all the corrections. Your response is inadequate in that you do not ensure accurate, complete, and current documentation. Please provide copies of policies, procedures, and training with expected completion dates that are being developed and implemented to ensure proper documentation of study data.

There must be a close cooperation and communication between all participants of the study, including the sponsor, the IRB, the investigator, and staff. If you or your staff completes any training please provide documentation and the dates of completion of any training specific for the conduct of clinical trials you and your staff have completed or plan to complete.

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 inspection report notes 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.

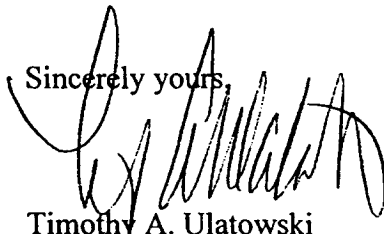
Within **fifteen (15) working days** of receiving this letter, please provide written documentation of the **actions** you have taken or will take to correct these violations and prevent the recurrence of similar violations in current or future studies for which you are the clinical investigator. In 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, the 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 the attention of: ~~XXXXXXXXXXXX~~, 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 Atlanta District Office. Please send a copy of your response to that office also.

If you have any questions, please contact [REDACTED] at [REDACTED], or at [REDACTED]

Sincerely yours,

A handwritten signature in black ink, appearing to read 'Timothy A. Ulatowski', written in a cursive style.

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