



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

OCT 9 2003

Via Federal Express
WARNING LETTER

Michael Feign, D.O.
Front Range Orthopedic, L.L.C.
1633 Medical Center Point
Colorado Springs, Colorado 80907

Dear Dr. Feign:

The purpose of this Warning Letter is to inform you of the objectionable conditions found during a Food and Drug Administration (FDA) inspection conducted at your clinical site and to discuss your written response dated June 11, 2003, to the deviations noted, and to request a prompt reply with regard to your corrective actions. The inspection took place during the period of April 14 through 24, 2003, and was conducted by Ms. Teena Aiken, an investigator from FDA's Denver District Office. The purpose of the inspection was to determine if your activities as a clinical investigator for [REDACTED] investigational study of the [REDACTED] complied with applicable FDA regulations. These products are devices as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act.

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 (510(k)) submissions 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 submitted by the district office revealed serious violations of requirements of Title 21, Code of Federal Regulations (21 CFR), Part 812- Investigational Device Exemptions and Part 50- Protection of Human Subjects, and Section 520(g) of the Act. You received a Form FDA 483, "Inspectional Observations," at the conclusion of the inspection that listed the deviations noted and discussed with you. The deviations noted on the Form FDA 483, our subsequent review of the inspection report, and your response to the Form FDA 483 items are discussed below:

- 1. Failure to maintain control of the device, failure to ensure that informed consent is obtained, and failure to report use of investigational device without informed consent to the sponsor and reviewing IRB (21 CFR 812.100, 21 CFR 50.20, and 21 C.F.R. 812.150(a)(5))**

On December 28, 2001, subject [REDACTED] was [REDACTED] with the investigational device. Subject [REDACTED] was not enrolled in the study and did not sign an informed consent form. You failed to maintain control of the investigational device, did not ensure informed consent was obtained prior to [REDACTED] the investigational device into subject [REDACTED] and did not report use of the investigational device to the reviewing IRB. In accordance with 21 CFR 812.100, investigators are responsible for: maintaining control of devices under investigation and must not supply an investigational device to any person not authorized to receive it. As required by 21 CFR 812.100 and 21 CFR 50.20, an investigator must ensure informed consent is obtained from subjects or the subject's legally authorized representative prior to his or her participation in an investigational study. If informed consent is not obtained because of emergency use, investigators are responsible for reporting use of the investigational device to the sponsor and reviewing IRB within five working days after the use occurs (21 CFR 812.150(a)(5)).

In addition, page three of the Investigator's Agreement has a statement of certification that written informed consent will be obtained from subjects or their legal representatives. You signed this agreement and are obligated to follow it, under 21 CFR 812.100.

Your response states that you were instructed by the sponsor to [REDACTED] subject [REDACTED] on a prescription basis. Also, you are following-up with subject [REDACTED]. Your response is not acceptable in that it does not adequately address the reasons for not enrolling [REDACTED] into the study, or how to avoid future deviations. FDA regulations do not provide for the "prescription" use of an unapproved device currently under IDE. Your records contain nothing to demonstrate that the investigational device was [REDACTED] in subject [REDACTED] in accordance with 21 CFR 812.36, FDA's regulations governing treatment use of an investigational device, and our records do not indicate that FDA has approved treatment use of this device.

- 2. Failure to conduct the study in accordance with the approved investigational plan and protocol, the investigator agreement, and any conditions of IRB approval; failure to obtain IRB approval of changes to informed consent forms (21 CFR 812.100 and 812.110(b); 21 CFR 50.27(a))**

On October 23, 2001, the Memorial Hospital IRB approved the investigational plan dated May 7, 2001, and a revised informed consent form (revision dated October 1, 2001) which is part of the investigational plan and protocol. Correspondence that you received from the IRB clearly indicated that changes to the investigational plan or protocol should be reported to the IRB:

- The October 23, 2001, letter approving the initial protocol contains a statement for protocol changes to be reported to the IRB.
- The IRB's letter, dated August 27, 2002 contains a statement for your site to notify them of any changes to the protocol.

You failed to follow the protocol and IRB requirements in that:

- You did not notify the reviewing IRB of the October 5, 2001, and May 2, 2002, revisions to the informed consent forms. As a result, fifteen out of twenty-one patients signed a revised informed consent form that had not been approved by the IRB, as required by 21 CFR 50.27(a).
- You did not notify the reviewing IRB of several protocol changes with revision dates of August 29, 2001, October 5, 2001, November 12, 2001; and May 15, 2002.
- Subjects [REDACTED] and [REDACTED] did not meet the inclusion/exclusion criteria specified in the investigational plan. Your records contain evidence that they were included in the study.

On February 20, 2003, the FDA approved the use of a [REDACTED] with the investigational device. During the inspection, you mentioned that you used the [REDACTED], also known as the [REDACTED]. During the years 2001 and 2002, the [REDACTED] was not approved for use, was not a part of the investigational device, and was not included in the investigational plan. Any use of the [REDACTED] prior to FDA approval of a revised protocol permitting its use is considered a deviation from the investigational plan. Page three of the Investigator Agreement includes a statement that "all non-emergency deviations from the FDA approved investigational plan require prior approval from FDA, the sponsor, and the appropriate IRB." The Investigator Agreement also includes a statement that any deviation from the plan be reported to the IRB, sponsor, and FDA as soon as possible but not later than five working days. You did not receive approval to use the [REDACTED], nor did you report your usage of this [REDACTED] to any of these entities, and thus you did not follow the Investigator Agreement.

Your written response indicates that [REDACTED] (the sponsor) made changes to the informed consent form and you were not told to send the revised forms to your IRB. Your response is not acceptable, as it is your obligation to follow FDA regulations, the investigational plan, and IRB conditions of approval, regardless of whether or not the sponsor instructs you to take a particular action required by those authorities. Your response also does not adequately address the various changes to the protocol and [REDACTED], or how to avoid future deviations. Your clinical site received correspondence which instructed you to notify the IRB of any changes to the research study. In addition, the June 25, 2002 Continuing Review Report Form, with your signature, has a question about protocol changes. Your reply to the question is "N/A" which indicates not applicable or no changes to the research study although there

were changes made. During the inspection, you acknowledged your participation in changes to the [REDACTED]

In addition, your records contain evidence that subjects [REDACTED] and [REDACTED] did not meet the inclusion/exclusion criteria, yet they were included in the study. In your written response you state that subject [REDACTED] was never enrolled into the study but was assigned a number by mistake, and that case reporting forms (CRFs) were started but that the subject was excluded from the study based on an excessive body mass index. Your response to this observation is inadequate in that you do not provide any corrective actions or details on how to avoid future deviations.

Your response for subject [REDACTED] states that [REDACTED]; at the time, was regarded as “at the same surgery.” On page two of the CRF #1, there is an exclusion criteria for [REDACTED]. As noted in the operative report, Subject [REDACTED] had a history of [REDACTED] and significant degeneration, and needed [REDACTED]. Your response to these observations is inadequate in that you do not provide any corrective actions or details on how to avoid future deviations.

In order to protect the rights, safety, and welfare of subjects under an investigator’s care, clinical investigators are required to ensure that investigations are conducted according to the signed agreement, the investigational plan and applicable FDA regulations (21 CFR 812.100 and 812.110(b)).

3. Failure to adhere to informed consent requirements (21 CFR 812.100, 21 CFR 50.20, 50.25(a), 50.25(b)(2) and 50.27)

A review of the informed consent forms at your study site revealed that the informed consent forms revised June 15, 2001, and July 5, 2001; and May 15, 2002 did not contain a description of the [REDACTED] procedures, contact information pertaining to research and research-related injury, witness information or signatures; or a statement of anticipated circumstances of subject’s possibility of termination by the investigator. A few examples follow:

- For subjects [REDACTED] and [REDACTED], contact information on the informed consent forms was blank. The IRB and investigator information was missing on subject [REDACTED] informed consent form.
- For Subjects [REDACTED] and [REDACTED], informed consent forms did not have any witness information or witness signature.

Further, subject signatures on several informed consent forms preceded the version date listed on that form. For example, the informed consent form signed by subject [REDACTED] has a version date of April 8, 2003, but the subject signed the informed consent form on March 20, 2003. Subject [REDACTED] signed an informed consent form on April 3, 2003 but the version date was April 8, 2003.

In accordance with 21 CFR 812.100, clinical investigators are responsible for ensuring that informed consent is obtained in accordance with the regulations. Investigators must obtain informed consent from the subject or the subject's legally authorized representative prior to his or her participation in an investigational study (21 CFR 312.60). The basic required elements for informed consent are set forth in 21 CFR 312.62(a). An investigator is responsible for providing information including: a description of the procedures to be followed, contact information for research-related injury and questions, and anticipated circumstances under which a subject's participation may be terminated by the investigator (21 CFR 312.62(a)(1), 312.62(a)(7) and 312.62(b)(2)). Also, informed consent must be documented by the use of a written consent form approved by the IRB. 21 CFR 312.64(a). The fact that subjects signed the consent forms before the forms revision dates indicates that those versions of the consent form were not approved by the IRB when they were signed. Also, that form calls for witness signatures, and hence, if that form was approved by the IRB, documentation of witness signatures was required.

In addition, paragraph four of the Memorial Hospital IRB's Certification of Review form, dated October 23, 2001, has a statement that informed consent is to be given or read to the study subject prior to the subject's participation in the study. Your signature on the Investigator's Agreement indicates your understanding of FDA's regulations, the IRB and sponsor's policies and procedures.

Your written response states that contact information was not typed into one of the revised informed consent forms and that has since been corrected, and [REDACTED] sent the informed consent forms. You indicate that you do not know how subjects could have signed informed consent forms on dates that precede the version date printed on the form. Your response does not address all of the problems noted above, and does not address the failure to assure that the informed consent forms that you used were approved by the IRB. Although some corrective action was taken, your response does not have details of further corrective actions and how to avoid future deviations.

4. Failure to report unanticipated adverse device effects (21 CFR 812.150(a)(1))

You failed to report to the reviewing IRB the adverse events for subjects [REDACTED] and [REDACTED]. In addition, during the inspection Ms. Aiken discussed other unanticipated adverse events, as follows:

- subject [REDACTED]--development of pitting edema in lower extremities; and
- subject [REDACTED]--development post-operative of right [REDACTED] pain, redness, and swelling.

An investigator is required to report to the sponsor and to the reviewing IRB any unanticipated device effects as soon as possible, but in no event later than ten working days after the investigators first learns of the effect (21 CFR 812.150(a)(1)).

You indicated in your written response that subject [REDACTED] was examined, and the complaints were felt to be physiologic and part of the new [REDACTED] functions which are not a problem or complication. Your response is inadequate. In your written response, you do not provide any details about the reporting of all adverse events to the sponsor or IRB, or the steps your clinical site will take or have taken to avoid future deviations.

5. Failure to maintain accurate and complete device accountability and subjects' records (21 CFR 812.140(a)(2) and 812.140(a)(3))

A review of the subject files revealed that device accountability records, CRFs and adverse event forms were incomplete or not properly maintained. Deficiencies noted include:

- Failure to properly maintain accurate, complete, and current device accountability records. There were no [REDACTED] usage tickets for 22 out of approximately 34 subjects.
- Failure to record inclusion/exclusion information or to document range of motion. For example, the record for subject [REDACTED] contains no inclusion/exclusion documentation.
- Failure to complete operative reports. For example, for subjects [REDACTED] and [REDACTED] operative reports were blank or incomplete.
- Failure to maintain case history supporting data. For example, none of the medical records included the body mass of study subjects. A body mass greater than [REDACTED] is an exclusion criteria.
- Failure to maintain adverse event forms and case report forms. During the inspection, you were unable to provide the following items: adverse event form for subject [REDACTED]; six week CRF for subject [REDACTED]; CRF operative report and [REDACTED] usage ticket for subject [REDACTED]; second [REDACTED] replacement; and adverse event report for subject [REDACTED].

FDA regulations require investigators to maintain accurate, complete, and current records of receipt, use or disposition of the investigational device, and each subject's case history and exposure to the device (21 CFR 812.140(a)(2) and 812.140(a)(3)).

Your written response has a statement that not all of your office charts are complete but the study documents are complete; the protocol is lacking in how your personal files are to be maintained or how to document information; many of the entries in different ink were completed later; and you were not aware at the time that a separate form should have been completed. Your response does not adequately address the steps you will take or have taken to correct the deviations and avoid future ones.

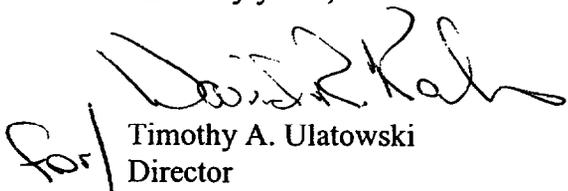
We do not intend the list of deviations noted above to be an all-inclusive list of deficiencies that may have existed in your clinical study.

During the close-out discussion, you acknowledged to Ms. Aiken that you did not have an adequate understanding of the regulations and you promised to notify the IRB of the changes in the protocol, informed consent form, [REDACTED], and [REDACTED] in patients not enrolled in the study. As a clinical investigator participating in an investigational device study, you are responsible for ensuring that adequate informed consent is provided to and obtained from study subjects participating in the study. Also, you are responsible for maintaining control of the investigational device and for ensuring that the investigation is conducted according to the investigational plan and applicable FDA regulations. To assist you, please refer to the complete guidance in the "FDA Information Sheets, Guidance for Institutional Review Boards and Clinical Investigators," and on the Internet at www.fda.gov/oc/ohrt/irbs/faqs.html#ClinicalInvestigations. Enclosed to assist you in better understanding of your responsibilities as a clinical investigator are copies of 21 CFR Parts 50, 56, and 812. These documents also are available electronically at www.access.gpo.gov/nara/cfr. Part 812 describes your responsibilities as a clinical investigator of an investigational device and Part 50 includes what is required to protect the welfare of study subjects. Part 56, Institutional Review Board, covers the responsibilities of IRBs and what an IRB expects from you as a clinical investigator, as well as their responsibilities to you.

Please inform us in writing within 15 working days of receipt of this letter, of the additional corrective actions you have taken or plan to take with regard to the deviations noted. Please send this information to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch II (HFZ-312), 2094 Gaither Road, Rockville, Maryland 20850, Attention Linda Godfrey. Failure to respond could result in regulatory action without further notice.

A copy of this letter has been sent to FDA's Denver District Office, Building 20, Denver Federal Center, Post Office Box 25087, Sixth Avenue and Kipling Street, Denver, Colorado 80225. We request that a copy of your response also be sent to that office. If you have any questions you may contact Linda Godfrey, telephone at (301) 594-4723, ext. 134.

Sincerely yours,


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

Enclosures

cc: (purged copies)

Memorial Hospital Institutional Review Committee
1400 East Boulder
Colorado Springs, CO 80909

