



JUN 28 2006

## WARNING LETTER

VIA FEDERAL EXPRESS

Scott A. Spiro, MD  
101 Old Short Road, Suite 510  
West Orange, NJ 07052

Dear Dr. Spiro:

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 21 through April 13, 2006, by an investigator from the FDA New Jersey District Office. The purpose of this inspection was to determine whether activities and procedures related to your participation in the clinical study titled [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.

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 several 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 FDA 483 and our subsequent review of the inspection report are discussed below:

- 1. Failure to ensure that informed consent was obtained in accordance with 21 CFR Part 50, and failure to ensure all required elements of informed consent were provided to study subjects [21 CFR 812.100, 21 CFR 50.20, 21 CFR 50.25(a)(7), and 21 CFR 50.27(a)].**

You failed to ensure that the current, IRB-approved version of the informed consent was executed by each of the subjects enrolled as required by the above-stated regulations prior to

their participation in the study. Examples of this failure include but are not limited to the following:

- a.) At least 38 of the 56 subjects enrolled in the study signed an unapproved version of the informed consent form. Specifically, the consent forms signed by these study subjects were not reviewed and approved by the Institutional Review Board (IRB) at your institution.

In addition, the 38 unapproved consent forms signed by study subjects were missing one or more of the basic elements required in informed consent. Specifically, the forms were missing an explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and/or an explanation of whom to contact in the event of a research-related injury to the subject.

- b.) One subject [REDACTED] signed the consent form after the study surgery was performed. Specifically, the subject's surgery was performed on 10/25/05, but the date of the subject's signature on the consent form is 3/14/06.

**2. Failure to ensure an investigation is conducted in accordance with the signed agreement with the sponsor, the investigational plan, applicable FDA regulations, and any conditions of approval imposed by FDA or the IRB [21 CFR 812.100, 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:

- a.) The IRB renewal of approval for the study was granted on 6/15/04 and extended only until 6/14/05. You were required to request renewed approval to continue your study after that time. You did not submit a request to obtain IRB approval to continue the study until 8/4/05. However, during the time the IRB approval had lapsed, you enrolled and/or performed study surgery on at least three subjects. Specifically:

- i. [REDACTED] was enrolled into the study and had the study surgery on 6/16/05.
- ii. [REDACTED] was enrolled into the study and had the study surgery on 6/20/05.
- iii. [REDACTED] was enrolled into the study and had the study surgery on 8/3/05.

- b.) The study protocol required that if an adverse reaction requires removal of an implanted prosthesis, the device must be returned to [REDACTED] for investigation and analysis by the Product Evaluation Department. At least two study subjects had their devices surgically removed due to adverse reactions, but the explanted devices were not returned to [REDACTED]. Specifically:

- i. Subject [REDACTED] that was implanted on 1/31/05 was surgically removed on 6/20/05, due to capsular contracture. There was no record that the explanted device was returned to [REDACTED].
- ii. Subject [REDACTED] that were implanted on 3/16/05 were surgically removed on 8/31/05, due to capsular contractures. There was no record that the explanted devices were returned to [REDACTED].

- c.) The study protocol required subjects to be followed post-operatively at specific time-points. There was no record that all subjects were seen as required. For example:
- i. Subject [REDACTED], whose study surgery was performed on 1/29/04, was not seen for the one-year follow-up visit until nearly two years after the surgery, on 1/17/06.
  - ii. Subject [REDACTED], whose study surgery was performed on 1/8/04, had no record of being seen for a follow-up visit.
- d.) The study protocol lists reportable adverse reactions, including device leaks, tears, or ruptures; surgical removal of the [REDACTED] due to leaks, tears, or ruptures; and all capsular contractures which result in surgical intervention. The protocol states that such events must be reported within 72 hours to the study sponsor, and must also be reported to the IRB. In addition, the study protocol requires that a serious adverse reaction, injury or effect, device malfunction, death or life-threatening occurrence that may be reasonably suspected of being associated with the study device be reported “immediately to [REDACTED] and the applicable IRB.” At least five adverse events that met the above criteria were not reported to the sponsor and/or IRB. Specifically:
- i. Subject [REDACTED] required surgical intervention at another hospital on 2/15/06 to remove [REDACTED]. At the time of the FDA inspection, this event had not yet been reported to the sponsor or the IRB.
  - ii. Subject [REDACTED] experienced [REDACTED] on 5/17/05, which required removal of the device on 6/20/05. The event was not reported to the study sponsor until 9/13/05, and at the time of the FDA inspection, had not yet been reported to the IRB.
  - iii. Subject [REDACTED] required surgical intervention at another hospital in July 2005 to [REDACTED]. The investigator was notified of the event on 10/7/05, but did not report it to the study sponsor until 10/21/05. At the time of the FDA inspection, this event had not yet been reported to the IRB.
  - iv. Subject [REDACTED] required surgical intervention to remove the [REDACTED] on 8/31/05 due to [REDACTED]. At the time of the FDA inspection, this event had not yet been reported to the IRB.
  - v. Subject [REDACTED] experienced [REDACTED] on 11/29/05, that will require surgical intervention to correct. At the time of the FDA inspection, this event had not yet been reported to the IRB.
- e.) The study protocol required that Case Report Forms (CRFs) be completed, reviewed by the clinical investigator, and forwarded to the sponsor within 10 working days of the study procedure. However, at least 35 subjects’ CRFs were forwarded to the sponsor several weeks or months after the study surgeries took place.
- f.) Consent form documents signed by study subjects were incomplete. Specifically:

- i. At least 11 consent forms signed by study subjects had blanks on the first page which were required to be completed with the name of the investigator, city, state, and subject's study number.
- ii. At least one consent form signed by a subject [REDACTED] had no investigator signature.
- iii. At least two consent forms signed by study subjects [REDACTED] had no witness signature.

**3. Failure to maintain accurate, complete, and current records regarding the receipt, use, or disposition of a study device [21 CFR 812.140(a)(2)].**

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

- a.) At the time of the FDA inspection, there were no device accountability records or device inventory records at your study site for 2004 and 2005. The staff delegated with the responsibility for maintaining the records stated that the original device accountability records were discarded after they were faxed to the study sponsor. The Device Inventory Records (DIRs) were forwarded to your site by the sponsor after the FDA investigator requested them during the FDA inspection.
- b.) At least 20 study devices that the FDA investigator observed in storage at your study site did not match the serial numbers of the devices listed as being on-site in the DIRs received from the study sponsor.
- c.) At least 7 study subjects' [REDACTED] were not documented on the DIRs received from the study sponsor.

**4. Failure to maintain accurate, complete, and current records of each subject's case history and exposure to the device [21 CFR 812.140(a)(3)].**

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

- a.) Consent form documents signed by study subjects contained revisions that raise questions about the accuracy of the records pertaining to each subject's case history and exposure to the device. Specifically:
  - i. At least two consent forms signed by study subjects ([REDACTED]) had the investigator's signature covered over with "white-out" and another signature over-written in the space.
  - ii. At least two consent forms signed by study subjects ([REDACTED]) had the date of the investigator's signature covered over with "white-out" and another date over-written in the space.
  - iii. At least three consent forms signed by study subjects ([REDACTED]) used an investigator signature stamp, instead of the actual investigator signature.
- b.) Operative Report Case Report Forms (CRF) contained revisions that raise questions about the accuracy of the records pertaining to each subject's case history and exposure

to the device. At least 4 subjects' Operative Report CRFs had your signature as Investigator with a date that was before the date of the surgeries documented on the forms. Specifically:

- i. Subject [REDACTED] study surgery was on 11/17/05, but you signed the Operative Report CRF on 7/29/05.
- ii. Subject [REDACTED] study surgery was on 4/21/05, but you signed the Operative Report CRF on 4/5/05.
- iii. Subject [REDACTED] study surgery was on 8/11/05, but you signed the Operative Report CRF on 8/2/05.
- iv. Subject [REDACTED] study surgery was on 6/2/05, but you signed the Operative Report CRF on 5/24/05.

c.) Case Report Forms (CRFs) were incomplete. For example:

- i. At the time of the FDA inspection, CRFs had not been completed for at least 2 subjects. Specifically:
  - a. Subject [REDACTED], whose surgery took place on 10/27/05, had no CRFs completed.
  - b. Subject [REDACTED], whose surgery took place on 10/25/05, had no CRFs completed.
- ii. Numerous subjects had incomplete information on the Preoperative Patient History Record CRFs, which were used to determine subject eligibility. For example:
  - a. At least 8 subjects' CRFs had no answer for the question documenting the reason the subject was not able to receive [REDACTED].
  - b. At least 6 subjects' CRFs had no date of birth recorded.
  - c. At least 6 subjects' CRFs did not have the subjects' height and weight recorded on the Physical Exam Results section.
  - d. At least 17 subjects' CRFs had no answer for whether a [REDACTED] was done.
  - e. At least 20 subjects' CRFs did not document [REDACTED] results.
  - f. At least 32 subjects' CRFs did not document [REDACTED] characteristics.
  - g. At least 11 subjects' CRFs did not document information about radiation therapy.
- iii. CRFs contained inconsistent or incorrect information. For example: For Subject [REDACTED] the date of surgery, according to the enrollment log, was 3/9/05. However, the CRFs for this subject reported the date of surgery as 2/6/05 or 11/25/47, and the date is not reported at all on the Registry Enrollment Form.

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.

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. 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.

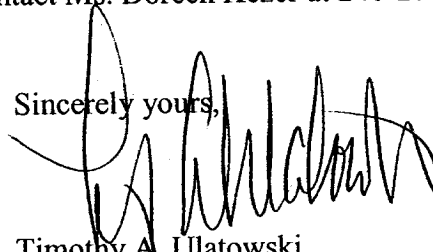
You will find information to assist you in understanding your responsibilities and planning your corrective actions in the FDA Information Sheets Guidance for Institutional Review Boards and Clinical Investigators, which can be found at <http://www.fda.gov/oc/ohrt/irbs/>. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. Please send your response to:

Food and Drug Administration  
Center for Devices and Radiological Health  
Office of Compliance, Division of Bioresearch Monitoring, HFZ-311  
9200 Corporate Boulevard, Rockville, Maryland 20850  
Attention: Ms. Doreen Kezer, Chief, Special Investigations Branch.

A copy of this letter has been sent to the FDA New Jersey District Office, 10 Waterview Blvd., Third Floor, Parsippany, NJ 07054. Please send a copy of your response to that office.

If you have any questions, please contact Ms. Doreen Kezer at 240-276-0125 or at [Doreen.Kezer@fda.hhs.gov](mailto:Doreen.Kezer@fda.hhs.gov).

Sincerely yours,

A handwritten signature in black ink, appearing to read "Timothy A. Ulatowski". The signature is fluid and cursive, with a large initial "T" and "U".

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