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

WARNING LETTER

Via Federal Express

JUN 13 2005

Richard Coutts, M.D.
8008 Frost St., Suite 300
San Diego, CA 92123-2712

Dear Dr. Coutts:

The purpose of this Warning Letter is to inform you of objectionable conditions revealed during a Food and Drug Administration (FDA) inspection of your clinical site and to request a prompt reply. During the period of December 20 through February 9, 2005, Mr. Thomas R. Beilke, an investigator from the FDA's Los Angeles District Office inspected your site. The purpose of the inspection was to determine whether your clinical site activities and procedures relating to investigational studies of FDA-regulated products complied with applicable FDA regulations. The product used in the [REDACTED] study sponsored by [REDACTED], is a device as that term is defined in Section 201(h) of the Federal Food, Drug, and Cosmetic Act [21 U.S. C. 321(h)].

We have completed our review of the report submitted by the Los Angeles District Office which described and documented deviations from the requirements of Title 21, Code of Federal Regulations (21 CFR), Part 56 - Institutional Review Boards, Part 50 - Protection of Human Subjects, and Part 812-Investigational Device Exemptions. These deviations were listed on the Form FDA 483, "Inspectional Observations," that was presented to and discussed with you and with Richard F. Santore, M.D., at the conclusion of the inspection.

The inspection was conducted under a program designed, in part, to ensure that data and information contained in applications for Investigational Device Exemptions (IDE) or Premarket Approval (PMA) are scientifically valid and accurate. Another objective of this program is to ensure that human subjects are protected from undue hazard or risk during the course of scientific investigations.

A description of the deviations from FDA regulations follows:

- 1. Failure to obtain IRB approval prior to allowing any subjects to participate in an investigation. [21 CFR 812.110(a)]**

Pursuant to 21 CFR 812.110(a), an investigator may determine whether potential subjects would be interested in participating but shall not allow any subject to participate before obtaining both IRB and FDA approval. Examples of this failure include but are not limited to the following:

The [REDACTED] of [REDACTED] Institutional Review Board ([REDACTED] IRB) notified you on June 5, 2000, July 17, 2000, and on September 12, 2000, that your study was conditionally approved pending the receipt of specified study materials. You failed to respond to these repeated requests. On October 16, 2000, the IRB, having received no response to its requests, inactivated the study and stated there was to be no further enrollment of subjects into the study; however, you enrolled two subjects into the study, one on December 21, 2001, and another on March 26, 2002. Neither of these subjects ([REDACTED] and [REDACTED]) was enrolled into an IRB approved study at UCSD.

2. Failure to maintain accurate, complete, and current records relating to an investigator's participation in an investigation including records of each subject's case history and records evidencing informed consent. [21 CFR 812.140(a)(3)(i)]

Pursuant to 21 CFR 812.140(a)(3)(i), a participating investigator shall maintain records of each subject's case history and exposure to the device. Case histories include the case report forms and supporting data including signed and dated consent forms. Documents evidencing informed consent shall be obtained prior to participation in the study and must comply with the provision of 21 CFR 50.27. Examples of this failure include but are not limited to the following:

- a. There were no records documenting informed consent for subjects [REDACTED], [REDACTED] and [REDACTED] for the institution in which they received their implant surgery. The consent documents used were approved by another institution.
- b. Subjects [REDACTED] and [REDACTED] signed consent forms that were apparently not approved by any IRB.
- c. Subject [REDACTED] signed an outdated consent form.
- d. Signed consent forms for subjects [REDACTED], [REDACTED], and [REDACTED] did not document the date (year) of completion.
- e. The signed consent form for subject [REDACTED] was not signed by the physician as required by the IRB.
- f. The physician's signature on the consent form for subject [REDACTED] predated the subject's signature by 12 days.

- g. The initials of subjects [REDACTED] and [REDACTED] on different pages of their respective consent forms were in different handwriting styles and seem not to have been entered by the patients each time.
- h. The consent form for Subject [REDACTED] (subject number [REDACTED]) was incorrectly identified as number [REDACTED].

The following subjects did not have signed source documents supporting specific subject observations:

- i. Case Report Forms (CRFs) for subject [REDACTED] did not have corresponding source documents confirming the baseline range of motion ([REDACTED]) data.
- j. CRFs for subject [REDACTED] did not have corresponding source documents confirming height, weight, and Trendelenburg's sign evaluations at the six-week or three-month follow-up.
- k. CRFs for subject [REDACTED] did not have corresponding source documents to confirm baseline ranges for ROM, limp, pain, and deformity evaluation. There were no 12-month source documents to confirm height, weight or Trendelenburg's sign evaluation.
- l. CRFs for subject [REDACTED] did not have corresponding source documents confirming baseline history, gait, pain, deformity, ROM, or medication. In addition, you failed to sign three of the seven baseline pages of the CRFs.

Source documents did not always agree with CRFs . For example:

- m. ROM values in the source documents for subjects [REDACTED] and [REDACTED] did not agree with the corresponding CRFs.
 - n. The case history source documents dated February 18, 2002 and January 14, 2004, for the case history for subject [REDACTED] do not agree with the CRFs.
 - o. The source document for subject [REDACTED] indicates the appointment of May 5, 2000, was cancelled; however, the CRF documents the subject's evaluation on that day.
 - p. Baseline evaluation ROM values in the source documents for subject [REDACTED] did not agree with the corresponding CRF.
3. **Failure to ensure that the investigation was conducted in accordance with the signed agreement and investigational plan. [21 CFR 812.100 and 110(b)]**

Pursuant to 21 CFR 812.100 and 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 rights, safety and

welfare of subjects. Examples of this failure include but are not limited to the following:

- a. At least 20 radiographs were not marked with the subject code and radiographic technique as required by protocol.
 - b. Magnification markers were not used as an aid in evaluation as required by protocol. While you state in your written response that you did not feel that markers were necessary, the protocol required them.
 - c. Radiographs for nine subjects with 24 follow-up radiographs were either missing or taken outside the timeframe required by protocol.
 - d. You did not perform a gross analysis of the explanted devices for subjects [REDACTED], [REDACTED], and [REDACTED] as required by protocol.
4. **Failure to prepare and submit complete, accurate and timely reports regarding the withdrawal of IRB approval. [21 CFR 812.150(a)(2)]**

Pursuant to 21 CFR 812.150(a)(2), an investigator shall report to a sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation. Examples of this failure include but are not limited to the following:

- a. [REDACTED] IRB notified you in a letter dated September 26, 2000, that your approval had expired and you must cease enrollment. There are no records to indicate that you notified the sponsor of the expiration of approval.
 - b. [REDACTED] IRB notified you in a letter dated October 16, 2000, that the study was considered to be inactive and that no subjects were to be enrolled. This lapse in study activity was not reported to the sponsor until after a sponsor site visit in April 2002.
5. **Failure to maintain accurate, complete and current records relating to records concerning adverse device effects. [21 CFR 812.140(a)(3)(ii)]**

Pursuant to 21 CFR 812.140(a)(3)(ii), an investigator shall maintain all relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated). Examples of this failure include but are not limited to the following:

Subject [REDACTED] reported adverse events experienced during the study by telephone. You did not document the reporting of these adverse events to the IRB and/or sponsor.

The deviations cited above are not intended to be an all-inclusive list of deficiencies at your site. As a clinical investigator, it is your responsibility to ensure that investigations that you participate in are conducted in accordance with applicable FDA regulations.

Within 15 days working days, you must respond to this letter in writing. Please provide written documentation of the specific steps you have taken or will take to correct these violations and prevent the recurrence of similar violations in current and future studies. In addition, please provide a list of your current investigational studies and include the name of the study sponsor and the date of IRB approval. You should be aware that FDA considers your actions to be serious violations of the law that may result in further regulatory action, including initiation of disqualification procedures, without further notice.

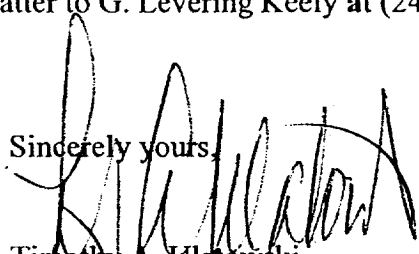
You should direct your response to the:

Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance
Division of Bioresearch Monitoring
Special Investigations Branch (HFZ-311)
2094 Gaither Road
Rockville, Maryland 20850
Attention: Mr. G. Levering Keely, BSN, MPA,
Consumer Safety Officer.

A copy of this letter has been sent to the Food and Drug Administration, Los Angeles District Office, 19701 Fairchild, Irvine, CA 92612. We request that a copy of your response also be sent to Los Angeles District Office.

Please direct all questions concerning this matter to G. Levering Keely at (240) 276-0254.

Sincerely yours,



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