DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

Via Federal Express

JUL 2 8 2004

WARNING LETTER

Timothy P. Mar, M.D.
2801 K Street, Suite 330
Sacramento, California 95816

Dear Dr. Mar:

This Warning Letter informs you of objectionable conditions found during a Food and Drug Administration (FDA) inspection conducted at your clinical site. This letter acknowledges your written response dated March 25, 2004, of your intent to clarify and/or respond to the noted violations. Your response indicates that you were in the process of reviewing each item listed on the Form FDA 483 and would provide a response within 30 days of the date of your letter; however, we have not received a written response which indicates the corrective and preventive actions that you have taken or will take. This letter requests that you implement prompt corrective actions to the violations cited. Mr. Jeffrey W. Shrifter, an investigator from FDA's San Francisco District Office, conducted the inspection from March 1 through 16, 2004. The purpose of the inspection was to determine if your activities as a clinical investigator (CI) for the [redacted] study complied with applicable FDA regulations. The [redacted] is a device defined in Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. 321 (h)].

The FDA conducted the inspection under a program designed to ensure that data and information contained in requests for Investigational Device Exemptions (IDE), Premarket Approval Applications (PMA), and Premarket Notification [510(k)] submissions are scientifically valid and accurate. The program also ensures that human subjects are protected from undue hazard or risk during scientific investigations.

Our review of the inspection report prepared by the district office revealed serious violations of Title 21, Code of Federal Regulations (21 CFR), Part 812-Investigational Device Exemptions, 21 CFR Part 50-Protection of Human Subjects, and Section 520(g) of the Act. At the conclusion of the inspection, Mr. Shrifter presented and discussed with you the observations listed on the Form FDA 483 "Inspectional Observations." The violations noted on the Form FDA 483 and our subsequent review of the inspection report are discussed below:

1. **Failure to ensure informed consent was obtained from all study subjects and failure to follow the Investigator's Agreement, Investigational Plan and applicable FDA regulations (21 CFR 812.100 and 812.110, 21 CFR 50.20, 50.25(a)(1) and 21 CFR 50.27(a))**

   In order to protect the rights, safety, and welfare of subjects under an investigator's care, Clinical Investigators (CIs) are required to ensure that investigations are conducted according to the following: the signed agreement, the Investigational Plan, and applicable FDA regulations. (21 CFR 812.100, 812.110(b)). CIs also must comply with any conditions of approval imposed by the Investigation Review Board (IRB) or FDA. (21 CFR 812.110(b)) Furthermore, the CI must ensure that informed consent is obtained from the subject or the subject's legally authorized representative prior to his or her participation in an investigational study, and that informed consent is documented by the use of written consent forms approved by the IRB. (21 CFR 50.20, 50.27(a) and 21 CFR 812.110(a)) The required elements for informed consent to which the CI must adhere are set forth in 21 CFR 50.25(a). The CI is also responsible for providing subjects a description of the procedures to be followed as set forth in 21 CFR 50.25(a)(l).

   You failed to satisfy these requirements. Examples of this failure include but are not limited to the following:

   - You failed to ensure that informed consent was obtained in accordance with both 21 CFR Part 50 and the Investigational Plan. For example, you did not ensure that Subject [redacted], who was implanted with the investigational device on September 24, 2002, signed an informed consent form. In addition, you allowed the sponsor's representative to discuss the study with Subject [redacted] prior to the subject signing the consent form, and allowed the sponsor's representative to conduct the consenting process with Subject [redacted] The sponsor's representative was not authorized to perform these functions.

   - You failed to ensure that the informed consent form included all the required elements. For example, the informed consent form approved by the [redacted] Institutional Review Committee ([redacted] IRC) did not contain a description of the randomization procedures as required by 21 CFR 50.25(a).

2. **Failure to obtain IRB approval prior to initiating the study (21 CFR 812.110(b))**

   Pursuant to 21 CFR 812.110(b) and Section 1 of the Investigator's Agreement, the CI must comply with any conditions of approval imposed by the IRB or FDA. The April 20, 2002 letter from the IRB states that "[a]ny changes to the protocol . . . must be approved by the IRC before they are implemented." You failed to obtain IRB

approval for the [redacted] revised protocol, dated June 17, 2002, prior to initiating the study and utilizing this protocol at your clinical site.

3. **Failure to follow the Investigator's Agreement, Investigational Plan and applicable FDA regulations (21 CFR 812.100, 812.110(a) 812.110(b))**

CIs are required to ensure that investigations are conducted according to the following: the signed agreement, the Investigational Plan, and applicable FDA regulations, as well as any conditions of approval imposed by the IRB or FDA pursuant to 21 CFR 812.100 and 812.110(b). The study protocol is part of the Investigational Plan. (21 CFR 812.25(b))

You failed to adhere to FDA regulations by failing to follow the study protocol. Examples of this failure include but are not limited to the following:

- The Inclusion/Exclusion Form for each subject reflects a "[redacted]" ([redacted]) of less than [redacted] However, you did not in fact perform the [redacted] inclusion criteria test on the subjects prior to implantation.

- The pre-operative x-rays (which assist in establishing baseline information) for Subjects [redacted] and [redacted] were taken more than [redacted] days prior to surgery which is in violation of the Patient Visit and Evaluation Schedule section in the study protocol.

- There were no pre-operative x-rays taken for Subject [redacted] which is in violation of the Patient Visit and Evaluation Section in the study protocol.

- The early post-operative, 3-month, 6-month or 12-month post-operative visit x-rays were not performed for Subjects [redacted] and [redacted] in violation of the Patient Visit and Evaluation Section in the study protocol.

- There were no 6-month or 12-month follow-up visits for Subjects [redacted] and [redacted] in violation of the study protocol.

- The 3-month follow-up visit for Subject [redacted] exceeded protocol timeframes in violation of the study protocol.

4. **Failure to prepare and submit complete, accurate, and timely reports to the sponsor and IRB, and failure to comply with the Investigator Agreement (21 CFR 812.150(a)(1) and 812.110(b))**

A CI is required to conduct the investigation in accordance with the signed agreement, the investigational plan, and other applicable FDA regulations. (21 CFR 812.110(b)) FDA regulations require that a CI submit to the sponsor and to 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 (21 CFR 812.150(a)(1)). The '[redacted]' section of the protocol states that all adverse events will be reported.

You failed to satisfy these requirements. Examples of this failure include but are not limited to the following:

- Adverse reaction reports were not submitted to the sponsor or IRB for Subjects [redacted] and [redacted].
- Adverse reaction reports were submitted to the sponsor and/or the IRB more than 10 working days after you became aware of the adverse reactions for Subjects [redacted] and [redacted].

5. Failure to maintain accurate, complete, and current study records (21 CFR 812.140(a)(2) and 812.140(a)(3))

FDA regulations require CIs 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 pursuant to 21 CFR 812.140(a)(2) and 812.140(a)(3).

You failed to satisfy these requirements. Examples of this failure include but are not limited to the following:

- There are no records of receipt or disposition of the investigational devices.
- The IRC contingency approval memorandum, dated May 3, 2002, was not maintained.
- From July 2002 through July 2003, the case report forms (CRFs) do not have any totals for the [redacted]
- Subject [redacted]'s name is missing from the informed consent form.
- The CRFs for Subjects [redacted] and [redacted] are incomplete, unsigned, or undated by the investigator.
- The early post-op follow-up x-ray evaluation CRFs are missing from the files for Subject [redacted]
- Subject [redacted] early post-op visit CRF is dated October 30, 2002, which is prior to the actual office visit on November 11, 2002.

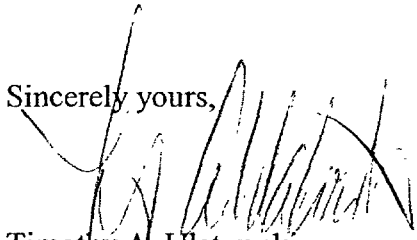
The above-described deviations are not intended to be an all-inclusive list of deficiencies that may exist in this clinical study. It is your responsibility as a CI to ensure adherence to each requirement of the Act and all applicable federal regulations. Please provide a list of your current investigational studies and include the name of the study sponsor and the date of IRB approval.

Within 15 working days after receiving this letter 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. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. 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.

Send your response to: 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.

We are also sending a copy of this letter to FDA's San Francisco District Office, and request that you also send a copy of your response to that office. If you have any questions, please contact Linda Godfrey by phone at 301-594-4723 extension 134 or by email at linda.godfrey@FDA.HHS.GOV.

Sincerely yours,



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

cc: (purged copies)

[redacted]

Institutional Review Committee

[redacted]

President/CEO

[redacted]