DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

JUL 19 2004

WARNING LETTER

VIA FEDERAL EXPRESS

Raul A. Marquez, M.D.
[redacted]
2402 Cornerstone
Edinburg, Texas 78539

Dear Dr. Marquez:

This Warning Letter informs you of objectionable conditions found during a Food and Drug Administration (FDA) inspection conducted at your clinical site. This letter also discusses your written response, dated May 7, 2004, to the noted violations and requests that you implement prompt corrective actions. Ms. Brenda Stewart-Munoz, an investigator from FDA's Dallas District Office, conducted the inspection from March 15 through 17, 2004. The purpose of the inspection was to determine if your activities as a clinical investigator for the [redacted] study complied with applicable FDA regulations. The [redacted] is a device as 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 and 21 CFR Part 50-Protection of Human Subjects, and Section 520(g) of the Act. At the close of the inspection, Ms. Stewart-Munoz presented a Form FDA 483 "Inspectional Observations" to you for review and discussed the listed deviations. The deviations noted on the Form FDA 483 and our subsequent inspection report review as well as your responses to the Form FDA 483 items are discussed below:

1. **Failure to ensure that informed consent is obtained from all study subjects and failure to follow the investigational plan (21 CFR 812.100, 812.110(b) and 21 CFR 50.20).**

   In order to protect the rights and welfare of research subjects, investigators are responsible for ensuring that informed consent is obtained from a subject or that subject's legally authorized representative prior to his or her participation in an investigational study. (21 CFR 812.100 and 21 CFR 50.20) Pursuant to 21 CFR 812.100 and 812.110(b), clinical investigators are required to conduct investigations according to the signed agreement, the Investigational Plan which includes the study protocol, applicable FDA regulations (including those governing informed consent) and any conditions of approval imposed by the IRB or FDA. In this case, the study protocol inclusion criteria section and investigator agreement have statements that written informed consent must be signed by a patient or family member with power of attorney.

   You failed to satisfy these requirements. An example of these failures includes but is not limited to Subject [redacted] being implanted with the investigational device on July 9, 2003, without signing an informed consent form.

   As of the date of your response, Subject [redacted] has signed an informed consent form, new procedures have been implemented, and your response included a copy of the Subject's consent form. This response appears adequate.

2. **Failure to conduct the study in accordance with the approved investigational plan and protocol and applicable FDA regulations (21 CFR 812.100, 812.110(b)); and failure to report and obtain prior sponsor approval of protocol deviations (812.150(a)(4)).**

   Pursuant to 21 CFR 812.100 and 812.110(b), clinical investigators are required to conduct investigations according to the investigational plan, which includes the study protocol, and applicable FDA regulations. Under 21 CFR 812.150(a)(4), except in an emergency necessitating a deviation to protect the life or physical well-being of a subject, prior approval by the sponsor is required for changes in or deviations from an investigational plan. (Emergency deviations must be reported to the sponsor and reviewing IRB no more than 5 days after they occur.)

   You failed to follow the study protocol which is a part of the investigational plan. There was no evidence that you received prior sponsor approval for these deviations. Examples of your failure to satisfy these requirements include but are not limited to the following:

- The Post Operative Subject Management section of the protocol states that "[redacted]." There was no evidence that you administered [redacted] in accordance with this protocol, and no evidence that you received prior permission from the sponsor to deviate or alter the protocol in this way.

  Your response indicates that [redacted] administration [redacted] days pre-operatively is not the standard of care for any surgical patient; your institutional practice is to administer [redacted] the day of surgery and [redacted] days post-operatively; you contacted the sponsor for directions and received guidance, and your site placed a "Note to the File" which acknowledges the oversight. However, this response does not indicate that you obtained sponsor permission prior to deviating from the investigational plan, nor does it demonstrate that these deviations met the criteria for emergency deviation. This response is inadequate, in that, it does not indicate how you will prevent these protocol deviations and reporting failures from recurring in the future. We note that during the close-out discussion, you stated that you used [redacted] pre- and post-operatively; and you indicated that you have a discharge sheet that shows the usage and it is maintained in the patients' hospital chart located at the hospital. If you contend that you did not in fact deviate from the protocol, please provide copies of the discharge sheets for each patient implanted with the investigational device with your response. (As addressed further below, clinical investigators are also required to maintain accurate, complete, and current records of a subject's case history and exposure to a device, under 21 CFR 812.140(a)(3), and such records should include the history of [redacted] administration required by the protocol.)

- The protocol states that subjects, who are enrolled in the study and require surgery on the [redacted], are acceptable as long as a period of [redacted] to [redacted] months has elapsed since the initial surgery on the [redacted]. Subjects [redacted] and [redacted] received the investigational device on their [redacted] before the acceptable time period dictated by protocol had elapsed. Also, the protocol indicates that subjects must be between [redacted] years old to be included in the study, however, Subject [redacted] was under the age of [redacted] and did not meet the protocol inclusion criteria, yet this subject was enrolled in the study. There is no indication that the sponsor was notified and gave permission for either of these deviations.

  Your written response to observation 2, item 2 on Form FDA 483 indicates that for future enrollment your site will do the following:

  - review the subject's history and the inclusion/exclusion criteria during each subject's pre-screen visit which could also be the pre-operative visit;

- if the subject meets the exclusion criteria at the time of the visit, the doctor will discuss postponing the procedure until they qualify for the investigational device or offer an approved device; and

- all staff members reviewing the subjects for participation and involved in the informed consent process have been informed and re-educated in the inclusion/exclusion criteria.

In addition, your response indicates that Subject [redacted] did not receive the investigational device; upon review of the patient's file it was determined that this Subject met multiple exclusion criterion; and that you have included with this response a "Note to the File" which states that no implantation occurred. This response appears to be adequate.

- The three month visit for Subject [redacted] and the three and six month visits for Subject [redacted] exceeded protocol timeframes.

  In your response, you indicate that you are implementing preventative actions by establishing a subject visit tracking system, confirming the spreadsheet with the monitor, and have plans to take measures to ensure that subjects are notified in a timely manner to schedule appointments. If implemented as described, your corrective actions appear to be adequate and will be verified during a future inspection.

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

FDA regulations require investigators to maintain accurate, current and complete records of each subject's case history and exposure to the device. (812.140(a)(3)).

Examples of your failure to satisfy these requirements include but are not limited to the following:

- Pre-operative case report forms (CRFs) for Subjects [redacted] and [redacted] were lacking source documentation for the [redacted] and [redacted] scores.

  Your response to observation 3, item 1 states the [redacted] and [redacted] assessments were entered directly on the CRFs; there is no source document to substantiate this information; the first version of the CRF #4 ([redacted] assessment) did not include a scoring mechanism and the sponsor has created a new CRF#4; and all of the above subjects' records have been reviewed for accuracy and confirmation of your site's findings. You included details of each subject's specific resolutions which indicate:

- That the [redacted] or [redacted] was not completed;
- That one or both tests were completed and the score was not calculated; and
- That all of the above subjects should not have been enrolled into the study.

Your response is inadequate, in that, all study records were not reviewed for accuracy and confirmation of findings to ensure adequate corrective actions.

- There were no CRFs and documentation in the patient charts of the immediate post-operative x-rays for all subjects.

  Your response indicates the following:

  - that the immediate post-operative x-rays were not made available during the inspection;
  - the x-rays were performed for all patients after surgery;
  - documentation for post-operative x-rays is located in the hospital medical records at your neighboring facility; and
  - duplicate copies of the x-rays are not maintained in the subjects' charts and are available from the hospital.

  Your response appears to be incomplete. Please provide FDA with a copy of the documentation for all subjects' post-operative x-rays and the steps you plan to take or have taken to prevent future recurrence of inadequacies with subject records.

- CRFs are incomplete for all visits by Subjects [redacted] and [redacted] CRFs are incomplete for the 3 month, 6 month, and 12 month visits by Subjects [redacted] and [redacted]

  Your response indicates that you are implementing preventative "practices" so this will not continue to be an issue in the future; all of the above subjects' CRFs have been completed; and future CRFs will be completed in a timely manner. In addition, you indicate that subject [redacted] did not receive the investigational device and CRF completion was not needed in this case. Your response is inadequate, in that, you do not indicate the specific steps or preventive practices which you are taking or have taken to prevent the recurrence of this deviation.

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 clinical investigator to assure adherence to each requirement of the Act and all applicable federal regulations. 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 Los Angeles 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