DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
9200 Corporate Blvd
Rockville, MD 20850

95517

OCT 11 2005

WARNING LETTER

VIA FEDERAL EXPRESS

Sheri L. Rowen, MD
Mercy Medical Center
514 Professional Building
301 St. Paul Place
Baltimore, Maryland 21202

Dear Dr. Rowen:

The purpose of this Warning Letter is to inform 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 June 30, 2005, to the noted violations and requests that you implement prompt corrective actions. An investigator from the FDA's Baltimore District Office conducted the inspection from May 12 through June 2, 2005. The purpose of the inspection was to determine if your activities as a clinical investigator for the study entitled [redacted] sponsored by [redacted] complied with applicable FDA regulations. [redacted] is a device as defined under Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. 321(h)].

The inspection was conducted under a program designed to ensure that data and information contained in applications for Investigational Device Exemptions (IDE), Premarket Approval Applications (PMA), or 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 report prepared by the Baltimore District Office revealed violations of Title 21, Code of Federal Regulations (21 CFR), Part 50 - Protection of Human Subjects, and Part 812- Investigational Device Exemptions. At the close of the inspection, the FDA investigator presented a Form FDA 483 "Inspectional Observations" to you for review and discussed the listed deviations with you and [redacted] Director, Regulatory Affairs, [redacted] participated by telephone. The deviations noted on the Form FDA 483, your response, and our subsequent inspection report review are discussed below:

Failure to provide adequate informed consent [21 CFR 812.100, and 21 CFR Part 50)]

As a clinical investigator you are responsible for ensuring that informed consent is obtained from each subject in accordance with 21 CFR Part 50 and the amended protocol for this study. The informed consent form (ICF) must be approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. Examples of your failure to comply with the informed consent and protocol requirements include, but are not limited to, the following:

Twenty-three out of forty-one study subjects were seen for four and five-year postoperative follow-up examinations without signing an amended approved ICF that included these visits. Specifically:

- Subject [redacted] had a five-year postoperative examination performed on the right and left [redacted] on [redacted] though the subject did not sign an approved ICF that included a five-year examination.
- Subject [redacted] had a four-year postoperative examination performed on both [redacted] on [redacted] and the five-year on [redacted] though the subject did not sign an approved ICF that included four- and five-year examinations.

In your response, you stated that you assumed that the ICFs were signed by the study subjects; however, as the clinical investigator, it is your responsibility to ensure that informed consent has been obtained before allowing any subject to participate in an investigation.

You stated that upon receipt of the IRB stamped ICF, you would mail the informed consent form to the subject and ask them to sign and request that they return the form to your office. For those subjects already seen, we suggest that the cover letter to this ICF include information that informs the subject that they should have been given the opportunity to sign an ICF prior to being seen for their follow-up examinations. Regarding subjects yet to be seen for their four and five year follow-up examinations, you stated that you and [redacted] will ensure that these subjects sign an informed consent prior to being seen. This response is partially acceptable; however, in addition to your stated action, we would like to see a written corrective action plan that describes how the informed consent process will be implemented at your study site to ensure that potential study subjects are appropriately consented prior to participation in a clinical study, and how that consent will be documented.

We feel it is important to inform you that issues concerning informed consent and maintaining complete, accurate, and current records relating to device accountability and recording data on CRFs were also discussed with you during the July 2003 inspection and relayed to you in FDA's letter to you dated May 19, 2004.

Failure to submit complete, accurate, and timely reports [21 CFR 812.150(a)(6)]

Investigators are responsible for submitting a final report to the sponsor and the IRB within three months of termination or completion of the investigation. You failed to adhere to this requirement when you failed to submit a final progress report to the sponsor and reviewing IRB in a timely manner. Specifically, the sponsor notified you in a letter dated [redacted] of the official closure of the investigation. You state in your response that you did not submit the final report to the sponsor and IRB until [redacted], which was well beyond the date of official closure of the investigation.

Failure to adhere to the general responsibilities of an investigator [21 CFR 812.100].

Investigators are responsible for ensuring that an investigation is conducted according to the signed agreement, investigational plan, and applicable FDA regulations. You failed to follow the study protocol, which is part of the investigational plan. Examples of your failure to comply with this requirement include, but are not limited to, the following:

- The study protocol requires using case report forms for 4 and 5-year postoperative examination results. The sponsor provided case report forms, for recording 4 and 5-year postoperative examination results, were not completed for all study subjects. Some subject data was recorded on the wrong version of the form. No forms were completed for the following subjects: Study subject [redacted] 4 and 5 year examination, and Study Subject [redacted] 4 year examination.

- The protocol requires that no part of the study "begin or be continued at any institution unless the IRB has provided written documentation to the Sponsor that it has reviewed and approved the study protocol and investigational plan, and that the same will be subject to continuing review and approval by that same IRB for the duration of the study, as required by 21 CFR 56." You conducted 4- and 5-year postoperative examinations prior to IRB approval of the amended protocol that included these examinations.

In your response, you stated that the four and five year follow-up examinations data for the study subjects were noted on source documents and will be transcribed to the CRFs and provided to the sponsor. This response is acceptable. However, you should understand that the CRFs are used as the means for recording data to be reported to the study sponsor, and subsequently to the FDA. Please provide a written corrective action plan that will be implemented at your study site to ensure that study data collected during future and other ongoing clinical studies are accurate and

complete, and that source data are accurately transcribed onto the CRFs. The above-described deviations are not intended to be an all-inclusive list of deficiencies that may exist in this clinical study. As a clinical investigator, it is your responsibility to ensure that you adhere to applicable FDA regulations.

Within 15 days working days after receiving this letter please provide written documentation of the additional 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. Your response should include a list of your current investigational studies with the name of the study sponsor and the date of IRB approval. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you.

You should direct your response to the Food and Drug Administration, Center for Devices and Radiological Health, HFZ-312, 9200 Corporate Boulevard, Rockville, Maryland 20850. Attention: Viola Sellman, Chief, Program Enforcement Branch

A copy of this letter has been sent to the Food and Drug Administration, Baltimore District Office, 6000 Metro Drive, Suite 101, Baltimore, Maryland 21215. We request that a copy of your response also be sent to the Baltimore District Office.

If you have any questions, please contact Ms. Sellman at (240) 276-0125, or by email at vxs@cdrh.fda.gov.

Sincerely yours,

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