DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

Via Federal Express

SEP 29 2005

WARNING LETTER

J. Rex Parent, M.D.
Fort Wayne Ophthalmology
321 E. Wayne Street
Fort Wayne, Indiana 46803

Dear Dr. Parent:

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. An investigator from the FDA's Detroit District Office conducted the inspection from May 25 through June 8, 2005. The purpose of the inspection was to determine if your activities as a clinical investigator for the [redacted] Device study, sponsored by [redacted] complied with applicable FDA regulations. The [redacted] is a device as that term is defined under 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), 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 inspection report submitted by the Detroit District Office revealed serious violations of Title 21, Code of Federal Regulations (21 CFR), Part 812 – Investigational Device Exemption. 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. The deviations noted on the Form FDA 483 and our subsequent inspection report review are discussed below:

Failure to adhere to the investigational plan (21 CFR 812.100 and 21 CFR 812.110(b)).

Pursuant to 21 CFR 812.100 and 812.110(b), clinical investigators are required to ensure that investigations are conducted according to the signed agreement, the investigational plan, and applicable FDA regulations, as well as any conditions of approval imposed by the IRB or FDA. In addition, federal regulations require that clinical investigators obtain prior approval from the sponsor before implementing any deviations from the investigational plan, except for deviations to protect the life or physical well being of a subject in an emergency. (21 CFR 812.150(a)(4)). If these changes or deviations affect the scientific soundness of the plan or

the rights, safety, or welfare of the subjects, FDA and IRB approval are also required. (21 CFR 812.150(a)(4), and 812.35(a)).

Our review of the inspection report revealed that you made numerous protocol deviations, with no indication that you notified the sponsor or IRB, much less obtained prior approval. These include, but are not limited to, the following:

- The protocol requires that the [redacted] be used for endothelial cell counts and to provide images of these cells. If any changes in equipment occur, approval from the sponsor is required. A review of the operator's manual revealed that the equipment used in this study was a [redacted] There was no approval by the sponsor for a change in equipment.

- The protocol indicates that calibration and validation for image quality of the [redacted] using the manufacturer's supplied calibration grid should be performed. Review of the inspection report revealed that the [redacted] was not calibrated and validated per the protocol.

- The preoperative or postoperative evaluations were not conducted for the following subjects:

  Subject [redacted]

  Best Corrected Visual Acuity (BCVA) and Uncorrected Visual Acuity (UCVA) were not performed as required on both eyes at the preoperative visit, the 1 week postoperative, and 1 month postoperative visits.

  Subject [redacted]

  Manifest refraction was not performed on the fellow eye at the 1 month postoperative visit on July 9, 2003.

- The protocol states that no Intraocular Pressure (IOP) reducing medications should be administered at any time during the postoperative course. If IOP-reducing medications are determined to be medically necessary, e.g. "if IOP $\geq$ 30 mm HG" and are administered, the exact type, dosage, and regimen should be documented and reported to the sponsor as an adverse event. Subjects [redacted] and [redacted] received IOP-reducing medications. There is no documentation that an adverse event was reported to the sponsor for these subjects.

- You failed to maintain a device accountability log, as specified in the study protocol, to track the lot number for each device used in the study and list the patient's name, identification number, and the date of surgery.

Failure to submit unanticipated adverse device effects (21 CFR 812.150(a)(1)).

- The [redacted]tudy protocol indicates that any unanticipated adverse events should be reported to the sponsor via an adverse event form. However, there is no record that any of the unanticipated adverse events documented on the Case Report Forms (CRF) were reported. These include, but are not limited to, the following:

  - On February 12, 2004, Subject [redacted] presented with cornea mild superficial punctuate keratitis (SPK) at 24 hours postoperative.

  - On December 16 and 17, 2003, Subject [redacted] presented with sub conjunctival hemorrhage (8 and 24 hours postoperative).

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

Pursuant to 21 CFR 812.140(a), clinical investigators must maintain accurate, complete, and current records relating to their participation in an investigation. These records must include records of each subject's case history and exposure to the device, including case report forms and supporting data, such as medical records. (21 CFR 812.140(a)(3)). You failed to satisfy these requirements, in that, a review of subject records revealed either the lack of protocol required data, discrepancies between the source documents (SD) and CRFs, or inaccurate or missing data regarding primary and secondary outcome variables indicated in the protocol. Examples of failure to satisfy these requirements include, but are not limited to, the following:

- Subject [redacted]

  There is no record in the SD of whether the subject was checked for iritis at each visit, even though the CRFs for all required visits (preoperative, 8 hour, 1 week, 1 month, and 3 month visits) indicate that this test was performed

- Subject [redacted]

  There are discrepancies/omission of data between the SD and CRF for BCVA and UCVA results during the visit on May 29, 2003. The SD for BCVA indicates 20/30 for the right eye (OD) and 20/20 for the left eye (OS); however, the CRF indicates 20/25 for the OD and 20/30 for the OS. An amended sheet of this form correctly documents the BCVA of 20/30 for the OD but the data for OS is indicated as "N/A."

In addition, your records must include record of receipt, use, or disposition of a device that relate to the type and quantity of the device; the dates of its' receipt; the batch number or code mark; the names of all persons who received, used, or disposed of each device; and why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of. (21 CFR 812.140(a)(2)). You failed to meet this requirement. For example:

- You did not maintain a device accountability log, as specified in the study protocol, to track the lot number for each device used in the study, list the patient's name, identification number, and the date of surgery. Therefore, the records of who received each study device were not current and readily available for review at the time of the inspection.

- In addition, correspondence from the study monitor dated August 20, 2003, indicates that 18 study device units should be returned and a replacement lot would be provided; however, there is no record indicating the return of any study devices.

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 ensure that you adhere to applicable FDA regulations.

Within fifteen (15) 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. Failure to respond to this letter and take appropriate corrective action could result in FDA taking regulatory action without further notice to you. In addition, FDA could initiate disqualification proceedings in accordance with 21 CFR 812.119. Please send your response to:

Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch (HFZ-312), 9200 Corporate Blvd., Rockville, Maryland 20850, Attention: Viola Sellman, Chief, Program Enforcement Branch.

We are also sending a copy of this letter to FDA's Detroit District Office, 300 River Place, Suite 5900, Detroit, Michigan 49207. We request that you also send a copy of your response to that 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