DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

95313d

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

WARNING LETTER

Via Federal Express

MAY 1 2005

Charles J. Winters, M.D.
[redacted]
19 Fontana Lane, Suite 206
Baltimore, Maryland 21237

Dear Dr. Winters:

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 January 25, 2005, to the noted violations and requests that you implement prompt corrective actions. Ms. Lynette P. Salisbury, an investigator from the FDA's Baltimore District Office, and Linda Godfrey, Consumer Safety Office with the Center for Devices and Radiological Health, conducted an inspection on December 6-8 and 14, 2004 and January 11, 2005. The purpose of the inspection was to determine if your activities and procedures as a clinical investigator for "[redacted]" clinical 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)], because it is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, or because it is intended to affect the structure or any function of the body.

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 Baltimore District Office revealed serious violations of Title 21, Code of Federal Regulations (21 CFR), Part 812 – Investigational Device Exemptions, and Part 50 – Protection of Human Subjects, and Section 520(g) of the Act. At the close of the inspection, Ms. Salisbury and Ms. Godfrey presented a Form FDA 483 "Inspectional Observations" to you for review and discussed the listed deviations with you and [redacted] The

deviations noted on the Form FDA 483, our subsequent review of the inspection report, and your response to the observations are discussed below:

1. **Failure to ensure that informed consent is obtained in accordance with 21 CFR Part 50; failure to ensure that the investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations. (21 CFR 50.20, 812.100, and 812.110(b)).**

   Pursuant to 21 CFR 812.100, an investigator is responsible for ensuring that informed consent is obtained in accordance with 21 CFR Part 50. The general requirements for informed consent are set forth at 21 CFR 50.20, which provides that "no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative.

   21 CFR 812.100 also requires an investigator to ensure that a study is conducted according to the signed agreement, the investigational plan, and applicable FDA regulations. The investigational plan includes the study protocol. (21 CFR 812.25(b)). The protocol for this study (Version [redacted] dated [redacted] at section [redacted] requires that the patient "[redacted]."

   Examples of your failure to comply with the informed consent requirements set forth in the FDA regulations and the study protocol include but are not limited to the following:

   - Of the [redacted] subjects who had screening examinations/tests, [redacted] (Subjects [redacted] and [redacted] did not sign an informed consent form (ICF) or screening consent form (SCF) prior to having [redacted] performed.
   - [redacted] subjects (Subjects [redacted], underwent study related procedures prior to signing the SCF or ICF.

   Your response is inadequate in that you have not provided the steps you plan to take to correct the recurrence of subjects having diagnostic procedures prior to signing ICFs or SCFs. Therefore, with your response to this letter, please include a detailed plan for how you will follow the study protocol related to obtaining informed consent or the screening consent for the "[redacted]" of this study and for any future studies, and please include a note in each affected subject's file related to this past deviation.

   In addition, there were no [redacted] obtained for Subjects [redacted] or [redacted] within the timeframes required in the protocol.

   Your response is inadequate in that you have not provided the steps you plan to take or have taken to correct or prevent the failure to conduct such procedures in the future. Please include a note in the files of Subjects [redacted] and [redacted] similar to the

note in the file of Subject [redacted], send a copy of the note with your response to this letter, report these protocol deviations to the sponsor and IRB, and provide detailed steps of how you plan to prevent the recurrence of this failure in the future.

2. **Failure to maintain accurate, current, and complete subjects' case history documents (21 CFR 812.100, 812.110(b), and 812.140(a)(3)).**

Pursuant to 21 CFR 812.140(a)(3), an investigator is required to maintain accurate, complete, and current records of each subject's case history and exposure to the investigational device. In addition, the protocol for the study states that an investigator is responsible for patient medical records. Your failure to adhere to this requirement includes but is not limited to the following:

The case history documents for all subjects were incomplete, not maintained, or non-existent. For example, there were no progress notes or previous medical histories of the subjects available for review. In addition, the diagnostic test results were not maintained at the investigator's site nor were they available for review.

Your response is inadequate in that you did not provide detailed steps of your corrective and preventative actions. In order to evaluate subjects for enrollment eligibility, your site would need to review diagnostic test results, such as [redacted] and [redacted] levels related to [redacted] Please provide detailed steps of how you plan to correct and prevent the recurrence of not maintaining case history documents. Although the subjects may state their health status orally, diagnostic tests provide confirmation and the results of such tests are important source documents when conducting studies.

3. **Failure to control the device under investigation and failure to maintain accurate, complete, and current records of receipt, use or disposition of a device (21 CFR 812.100, 812.110(b), and 812.140(a)(2)).**

Clinical investigators are required to maintain accurate, complete, and current records, including records of receipt, use or disposition of a device. (21 CFR 812.140(a)(2)). In addition, as noted above, clinical investigators are required to ensure that investigations are conducted according to the following: the signed agreement, the investigational plan (including the protocol), and applicable FDA regulations, as well as any conditions of approval imposed by the IRB or FDA. (21 CFR 812.100, 812.110(b)). The study protocol indicates that investigators are responsible for controlling the devices under investigation [redacted] and for records of device receipt, usage, and disposition of the device [redacted]. Examples of your failure to comply with these requirements include:

Device receipt, usage, and disposition records were not present at the clinical site; however, the sponsor notified you by letter dated September 6, 2003 of your

responsibilities for maintaining the investigational devices and related records. It appears that the sponsor's representatives completed and maintained records related to the investigational device.

We are concerned with the manner in which your site obtains the lot number of the device, completion of the product disposition log, and review of the records. For example, during the inspection, [redacted] stated that she would receive a call from [redacted] representative) and record the lot numbers on the case report forms; however, [redacted] indicated that he faxes the lot numbers to [redacted] stated that he completes the product disposition log with the lot number and the lot size at which time he then faxes the log to the sponsor and your office. Pages 4-9, 12-13, 16-17, and 19 of the product disposition log have the signature or initials of [redacted] (an employee of [redacted]). We cannot determine if the log was completed at the time of surgery or return of the device to the sponsor, the logs' accuracy, or if the responsibility for maintaining these records was delegated by you to the sponsor's representatives.

Your response is incomplete because it does not include a timeline for the development of a protocol related to receipt, use, and disposition of investigational devices. You stated in your response that the head nurse of the operating room will assist you in this matter. Please provide a timeline for when this protocol will be available and submit the timeline along with your response to this letter. Also, please include in your response or protocol how you plan to ensure that all investigational devices are controlled, as well as the accuracy and maintenance of records of receipt, usage, and disposition of the investigational devices.

The above-described deviations are not intended to be an all-inclusive list of deficiencies that may exist at your clinical site. It is your responsibility as a clinical investigator to assure adherence to each requirement of the Act and all applicable federal 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. 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.

Please provide a list of your current investigational studies and include the name of the study sponsor and the date of IRB approval.

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), 2094 Gaither Road, Rockville, Maryland 20850, Attention: Viola Sellman, Chief, Program Enforcement Branch.

We are also sending a copy of this letter to FDA's Baltimore District Office, 6000 Metro Drive, Suite 101, Baltimore, Maryland 21215. 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