DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

JAN 2 3 2003

WARNING LETTER
Via Federal Express

Douglas P. Sinn, D.D.S.
University of Texas
Southwestern Medical Center at Dallas
5323 Harry Hines Boulevard
Dallas, Texas 75390-9109

Dear Dr. Sinn:

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, to discuss your written response to the deviations noted, and to request a prompt reply with regard to the remaining issues. The inspection took place during the period of September 9 through 19, 2002, and was conducted by Ms. Cynthia A. Harris, an investigator from FDA's Dallas District Office. The purpose of the inspection was to determine if your activities as a clinical investigator in [redacted] study comply with applicable FDA regulations. This [redacted] is a device as that term is defined in Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

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

Our review of the inspection report submitted by the district office revealed serious violations of requirements 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. You received a Form FDA 483, "Inspectional Observations," at the conclusion of the inspection that listed the deviations noted and discussed with you. We acknowledge receipt of a copy of your response to Mr. Michael Chappell, District Director, Dallas District Office, dated October 7, 2002. The deviations noted on the Form FDA 483, our subsequent review of the inspection report, and your response to the Form FDA 483 items are discussed below. The deviations noted include:

Failure to obtain signed and dated informed consent documents from all study subjects prior to participation in the study. (21 CFR 812.100 and 50.20)

The investigational report notes that no informed consent document was located for subject [redacted] during the inspection. In addition, at least two (2) other subjects

([redacted] and [redacted]) did not sign an informed consent document until after initiation of their participation in the study. An investigator is required by 21 CFR 812.100 to ensure that informed consent is obtained according to 21 CFR Part 50. According to 21 CFR 50.20, no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative.

You state in your response that both you and the sponsor believe obtaining informed consent on the date of surgery, prior to the procedure, is acceptable. As stated above, 21 CFR 50.20 requires that an investigator obtain informed consent prior to involving a human being as a subject in research. FDA considers a subject to be involved in research once any information is collected from or about the subject that is required for participation in a study.

Failure to conduct the study in accordance with the investigational plan. (21 CFR 812.100 and 812.110(b))

Inspectional findings revealed that 14 of the 41 subjects treated at the time of the inspection missed one or more of the follow-up visits required by the study protocol. Moreover, the Visual Analog Scale (VAS) scores for [redacted] were not indicated on a line scale by the subject. In addition, one of the subjects [redacted] was included despite meeting one of the exclusion criteria, use of chronic steroid therapy. An investigator is required to conduct an investigation in accordance with the investigational plan.

Your response states that reminder calls were made to subjects for follow-up visits but were not documented. You further state that you cannot be responsible for subjects who miss their follow-up visits. When information is missing on a study subject that is essential to the support of a marketing submission, the sponsor may not have adequate information to support the submission. In addition, the subject has been unnecessarily exposed to the risk associated with the use of an investigational product. Subjects have the right to cease participation in a study at any time. However, it is a clinical investigator's responsibility to explain to potential subjects, during the informed consent process, the importance of meeting the study requirements. Only subjects willing and able to meet the study requirements should be encouraged to participate in the study.

Regarding the subject included despite chronic steroid therapy, you state in your response that the sponsor was concerned with transplant patients, as high levels of steroid treatment could lead to avascular necrosis. You state that the levels of Prednisone used by your subject were not inconsistent with the protocol's intent and that you have documented your explanation in a letter to the sponsor, a copy of which you have placed in the subject's file. Inclusion of this subject in the study is considered a deviation from the study protocol. Concurrence from the sponsor should have been obtained and documented prior to inclusion of this subject in the study.

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

A review of the subjects' medical records revealed that there was no information on study forms regarding complications and/or adverse reactions suffered by 12 subjects during the study or the intra-operative complications suffered by 2 subjects. An audit of the case report forms against the source documents also revealed several discrepancies in the data. An investigator is required to maintain accurate, complete, and current records of each subject's case history and exposure to the device.

Your response states that the complications/adverse events listed on the Form FDA 483 as missing from the study forms were outcomes expected within the first six months post-operative. However, it is essential to record all complications/adverse events that occur for study subjects. It is only when the sponsor is able to look at all such events that occur across the study that conclusions can be made regarding any connection between the events and use of the device. For example, use of a device could result in a higher or more serious incidence of complications than normally seen for similar procedures, which only a complete picture of all study complications would reveal.

With regard to missing x-rays, your response states that personnel may have removed them from the files for patient management purposes and mislaid them in the process. It is your responsibility as the clinical investigator to ensure that all study information is maintained in the study files.

Failure to use the institutional review board (IRB) approved informed consent form for all study subjects (21 CFR 50.27)

The inspection report notes that 2 subjects signed an informed consent document that had not been approved by the IRB and at least 15 subjects signed expired versions of the informed consent document. As stated in 21 CFR 50.27, informed consent must be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative.

Also discussed during the inspection was the enrollment of subjects into the study during a lapse in IRB approval, lack of documentation of IRB approval of the second protocol amendment, lack of phone logs of interactions with the sponsor; and failure to update the informed consent document to show the true size of the study.

The deviations listed above are not intended to be an all-inclusive list of deficiencies that may exist in your clinical study. It is your responsibility as a clinical investigator to ensure that an investigation is conducted according to the signed agreement, the investigational plan, and applicable FDA regulations.

Please inform us, within 15 working days of receipt of this letter, of the corrective actions you have taken or plan to take to ensure that the deviations noted are not repeated in future studies. Please send this information to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch II (HFZ-312), 2098 Gaither Road, Rockville, Maryland 20850, Attention: Jean Toth-Allen, Ph.D. Failure to respond could result in regulatory action without further notice, including initiation of investigator disqualification procedures.

A copy of this letter has been sent to FDA's Dallas District Office, 4040 North Central Expressway, Suite 300, Dallas, Texas 75204. We request that a copy of your response also be sent to that office.

If you have any questions, feel free to contact Dr. Toth-Allen at (301) 594-4723, ext. 141.

Sincerely yours,

Tim Ulatowski
Director
Office of Compliance
Center for Devices and Radiological Health

cc:

[redacted]