DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Blvd.
Rockville MD 20850

APR - 7 2008

WARNING LETTER

VIA FEDERAL EXPRESS

Wilson T. Asfora, MD
Sanford Clinic Neurosurgery & Spine
North Center, Suite 104
1210 West 18th Street
Sioux Falls, SD 57107

Dear Dr. Asfora:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection conducted at your clinical site from November 26 through December 27, 2007, by an investigator from the FDA Minneapolis District Office. The purpose of this inspection was to determine whether activities and procedures related to your participation as a sponsor and as a clinical investigator in the study titled *IDE Study for* under IDE complied with applicable federal regulations. The used for this study is a device as that term is defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 321(h). This letter also discusses your February 6, 2008, written response to the observations noted at the time of the inspection, and requests that you promptly implement corrective actions.

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 submissions (510(k)) 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 prepared by the district office revealed several serious violations of Title 21, Code of Federal Regulations (21 CFR) Part 812 - Investigational Device Exemptions. At the close of the inspection, the FDA investigator presented a form FDA 483 – "Inspectional Observations" for your review, and discussed the observations listed on the form with you. The deviations noted on the FDA 483 and our subsequent review of the inspection report and your written response to the FDA 483 are discussed below:

1. **Failure to ensure an investigation is conducted in accordance with the investigational plan, applicable FDA regulations, and any conditions of approval imposed by FDA or the IRB [21 CFR 812.100, 21 CFR 812.110(b)].**

   You failed to adhere to the above-stated regulations. Examples of this failure include but are not limited to the following:

   a.) Several subjects enrolled into the study do not appear to have met the eligibility criteria, as specified by the study protocol, and there was no evidence in your study files that you evaluated their eligibility. For example:

      i. At least 3 subjects had a documented history of prior to study enrollment. The study protocol prohibits subjects with It should also be noted that subject experienced immediately following the study procedure, and required of an

      ii. At least 6 subjects had a documented history of The study record for subject states.

      The study protocol prohibits subjects that

      Subject assessments of and are primary outcome measurements for this study.

      iii. At least 3 subjects had a documented history of and at least 1 subject had a documented history of

      The study protocol prohibits subjects that

   In your response to the FDA, dated February 6, 2008, you stated that you "will review the specific subjects identified and will respond accordingly", and that enrollment was suspended on December 1, 2006. This response is not acceptable in that you have not provided a corrective and preventive action plan to ensure that ineligible subjects are not enrolled into this and other studies in the future. Please also explain and provide documentation of the particular methods or procedures that will be used at your clinical site to train all study staff on any new procedures you may implement to correct this deficiency. You should also be aware the subjects listed above are examples of enrollment violations identified at your site, and is not an all-inclusive list.

   b.) The study protocol requires that all medical complications, whether device related or not, be documented. In addition, the for the study requires detailed descriptions of adverse events and complications, and requires information on corrective actions and outcome. These forms were incomplete for subjects reviewed by the FDA investigator, and contained only abbreviated descriptions of events and complications on the backs of the forms, with no other information.

   In your response, you stated that a separate Patient Adverse Event/Complication

Form for each patient for each visit will be completed and that the Study Monitor will sign and date each form. This response is not acceptable, in that you have not provided a timeframe in which this corrective action plan will be implemented. Please also note that, as the clinical investigator, you are responsible for reviewing and evaluating adverse events and complications. Having the study monitor sign and date each form does not verify that you, as the clinical investigator and a physician, have evaluated the adverse events. Please provide us with copies of the corrected Adverse Event/Complication forms, and please also explain and provide documentation of the particular methods or procedures that will be used at your clinical site to train all study staff on any new procedures you may implement regarding recording of adverse events.

c.) You did not use the study device in the manner specified by the protocol. Specifically, Subject did not have the required and experienced continuing resulting in The subject subsequently withdrew from the study. The study protocol specifically states,

d.) Serious Adverse Events and Complications were not reported to the IRB, as required by the study protocol and the IRB instructions. For example:

i. Subject experienced one day following of the study device.
ii. Subject experienced requiring intervention to

In your response, you stated that the previous study monitor/coordinator did not fulfill his responsibilities, and a new coordinator took over the role on June 1, 2007. This response is not acceptable in that you have not provided a corrective and preventive action plan to ensure that all adverse events and complications are reported to the IRB according to the study protocol and IRB requirements for this study and for other studies in the future. Please also be aware that, as a Clinical Investigator, you are responsible for ensuring that all study staff are adequately trained and qualified to perform study tasks delegated to them. You may delegate study tasks to other qualified personnel, but you may not delegate your responsibility to ensure that all study tasks are correctly performed. Please explain and provide documentation of the particular methods or procedures that will be used at your clinical site to train all study staff on any new procedures you may implement regarding required reporting of adverse events.

2. Failure to maintain accurate, complete, and current records relating to an investigation [21 CFR 812.140(a)].

FDA regulations require that Clinical Investigators maintain accurate, complete, and current records of each subject's case history and exposure to the device [21 CFR 812.140(a)(3)]. You failed to adhere to the above-stated regulation. Examples of this failure include but are not limited to the following:

a.) There was no documentation in any of your study records for the subjects reviewed by the FDA investigator to indicate that you evaluated their eligibility for the study prior to their enrollment. None of the clinic records contained source documentation or medical history records to verify the subjects met the enrollment criteria specific to the study,

In your response, you stated that you will attempt to collect all This response is not acceptable, in that you have not provided an explanation or documentation of particular methods or procedures that will be used at your clinical site to ensure that all required records are obtained and reviewed for study subjects in this and future studies. Please also provide information on any training for your study staff on any new procedures you may implement regarding review and maintenance of complete study records.

b.) All study data are handled and controlled by your Study Coordinator, who enters the data into an electronic data base. There is no audit trail or log of data changes that are made to the information in the database. Data cannot be verified against source records, since such records are not maintained.

3. **Failure to ensure proper monitoring of a clinical investigation [21 CFR 812.40].**

As a sponsor, you are responsible for submitting written procedures for monitoring the investigation and for ensuring proper monitoring of the investigation by adequately qualified and trained monitors. The monitoring plan included in your investigational plan states that the monitor will

and

There are no records to indicate that the study monitor verified the eligibility of the subjects listed in **citation 1a** above, who did not appear to meet the enrollment criteria for the study. There are also no monitoring records to show that the protocol violations cited above in **citations 1 and 2** were observed by the study monitor or that any actions were taken to correct the observed violations, or that unanticipated adverse events were evaluated.

Please provide us with documentation of a corrective action plan that addresses each of the violations noted above, such as a written procedure for ensuring study protocol compliance, written verification of training of all study staff on study procedures and requirements, a plan for ensuring accurate and complete study subject records and adverse events, ensuring proper monitoring of the study, and that corrective actions have been or will be implemented to prevent recurrence of the problems for these and future studies.

The violations described above are not intended to be an all-inclusive list of problems that may exist with your clinical study. It is your responsibility as a clinical investigator to ensure compliance with the Act and applicable regulations.

Within **fifteen (15) working days** of receiving this letter, please provide written documentation of the actions you have taken or will take to correct these violations and

prevent the recurrence of similar violations in current or future studies for which you are the clinical investigator and/or sponsor. In addition, please provide a complete list of all clinical trials in which you have participated for the last five years, including the name of the study and test article, the name of the sponsor, the number of subjects enrolled, and the current status of the study.

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.

You will find information to assist you in understanding your responsibilities and planning your corrective actions in the FDA Information Sheets Guidance for Institutional Review Boards and Clinical Investigators, which can be found at http://www.fda.gov/oc/ohrt/irbs/. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. Please send your response to:

Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Bioresearch Monitoring, HFZ-311
9200 Corporate Blvd., Rockville, Maryland 20850
Attention: Ms. Doreen Kezer, MSN, Chief, Special Investigations Branch.

A copy of this letter has been sent to FDA's Minneapolis District Office, 212 3rd Avenue South, Minneapolis, MN 55401. We request that a copy of your response also be sent to that office.

If you have any questions, please contact Ms. Doreen Kezer, MSN, at 240-276-0125 or at Doreen.Kezer@fda.hhs.gov.

Sincerely yours,

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