



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

WARNING LETTER

VIA FEDERAL EXPRESS

FEB 21 2006

Teck Mun Soo, M.D.
Michigan Spine and Brain Surgeons
22250 Providence Dr. Suite 601
Southfield, MI 48075

Dear Dr. Teck Soo:

This Warning Letter is to inform you of objectionable conditions observed during a Food and Drug Administration (FDA) inspection conducted at Michigan Spine and Brain Surgeons on October 20, 21, 24, 25, 27, and November 1, 2005, by an investigator from the Detroit District Office. This letter also discusses your written response to the noted violations dated November 15, 2005, and requests that you implement prompt corrective actions. The purpose of this inspection was to determine whether your activities and procedures related to your participation in the clinical study, [REDACTED]

[REDACTED], complied with applicable federal regulations. The [REDACTED] is a device defined in 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 requests for Investigational Device Exemptions (IDE), Premarket Approval Applications (PMA), 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 prepared by the district office revealed serious violations of Title 21, Code of Federal Regulations (21 C.F.R.), Part 812-Investigational Device Exemptions and Part 50-Protection of Human Subjects. At the close of the inspection, the FDA investigator presented an inspectional observations Form FDA 483 for your review and discussed the observations listed on the form with you. The



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deviations noted on the FDA 483, your written response and our subsequent inspection report review are discussed below:

Failure to ensure an investigation is conducted in accordance with the signed agreement with the sponsor, the investigational plan, and applicable FDA regulations. [21 CFR 812.100 and 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:

- 1) You failed to report serious adverse effects in accordance with the investigational plan which stated that all serious and unanticipated adverse events and effects were to be reported to the sponsor within 48 hours of becoming aware of the event and within 5 days of becoming aware of the event a facsimile or copy of the associated adverse event case report form (CRF) must be provided to the sponsor.
 - A) During surgery on [REDACTED] subject [REDACTED] experienced the following events; [REDACTED] requiring repair during surgery, fever of 102.5 from 12/2-12/5/2004, and a hematocrit level of 29.1 on 12/5/04. These events were not reported to the sponsor until 10/20/2005, in preparation for the FDA audit.
 - B) During surgery on [REDACTED] subject [REDACTED] experienced a vascular injury requiring repair during surgery; however, this adverse event was not reported to the sponsor until 6/3/2005 and to the IRB until 10/18/2005.
 - C) Subject [REDACTED] experienced the following events, documented in the case report form (CRF)/Questionnaire on 3/10/2005; aching back pain and non-descript shooting pain into the bilateral buttocks and sacrum, increased visual analogue scale (VAS) right leg pain > 30 points, severe right knee pain that worsened with bending. However, all these events were not reported to sponsor until 10/19/2005.

In your response you state, you considered these events as anticipated events from the procedure. You also note you discussed the definition of adverse events and reporting criteria in a staff meeting. When conducting a clinical investigation it is essential to document and report adverse events in accordance with the investigational plan and applicable regulations. Your response is incomplete, in that it does not describe a plan for assessment, documentation, and reporting of adverse events or dates when this action will be implemented to avoid future violations. Please provide copies of policies and procedures, with expected completion dates that are being developed and implemented to ensure documentation and reporting of adverse device effects are in accordance with the investigational plan, IRB policy, and applicable federal regulations.

- 2) You failed to complete diagnostic tests and procedures in accordance with the investigational plan.
 - A) The protocol required radiographic films showing AP view, AP right and left bending, lateral, flexion, and extensions to be performed within 3

months of enrollment. This combination of radiographic views was not performed on any of the [REDACTED] subjects enrolled.

- B) There were multiple subjects that had MRIs performed outside the 6 month window such as: subject [REDACTED], MRI was performed on 10/26/2003; surgery date was [REDACTED] which was well beyond the 6 month window.

In your response you note, you considered these x-rays as not standard care for patients undergoing surgery, so they were not obtained. These subjects were not undergoing standard surgery; they were enrolled in a clinical investigation in order to evaluate the safety and effectiveness of an investigational device and the additional x-rays are required by the investigational plan. In your response you stated, you discussed obtaining all x-rays at study visits in a research meeting. This response is inadequate in that it does not discuss steps you and your staff are taking to ensure study subjects receive all diagnostic tests and exams in accordance with the investigational plan. Please provide copies of policies and procedures, with expected completion dates that are being developed and implemented to ensure diagnostic exams are performed in accordance with the investigational plan.

In non-emergency situations, deviations from the investigational plan that could have affected the rights, safety, or welfare of human subjects were initiated without prior approval of the changes from the IRB. [21 CFR 812.150(a)(4)]

An investigator is responsible for notifying the sponsor and the reviewing IRB of any deviations from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan. If these changes or deviations affect the scientific soundness of the plan or rights, safety, or welfare of human subjects, FDA and IRB approval is required in accordance with 812.35(a).

You failed to secure IRB and sponsor approval of deviations in non-emergency situations prior to treating the subjects. Examples of your failure to comply with the above stated requirement include, but are not limited to the following:

- 1) Subject [REDACTED] had reported grade 1 spondylolisthesis, which is an exclusion criteria for the study. The subject subsequently experienced a grade 1-2 slip of the [REDACTED] and had revision surgery [REDACTED] on [REDACTED]. A protocol deviation report was not sent to the sponsor until 3/4/05 and to the IRB on 10/18/05. In addition, the serious adverse event (SAE) form was not filed with the sponsor until 4/18/2005.
- 2) Subject [REDACTED] was enrolled on 7/10/2004 and had a [REDACTED] procedure less than 30 days prior. Exclusion criteria, #19 states “subject has had surgical procedure requiring general anesthesia...that would increase the risk of DVT within the last 30 days”. This deviation was not reported to the sponsor until 10/18/2005 which is well beyond a full year since the date it occurred.

In your response, you did not discuss ensuring subjects met eligibility criteria. Please provide copies of policies and procedures, with expected completion dates, that are being developed and implemented to ensure eligibility of subjects, documentation of eligibility, and reporting of deviations to all applicable authorities.

Failure to properly document informed consent for 10 of [REDACTED] subjects. [21 CFR 50.27(a)]

Informed consent shall 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 legal representative at the time of the consent. Your study coordinator dated consents for the subjects. In addition, the FDA investigator observed that subject 11's consent document had the date the subject signed the document covered with "white-out" and a new date written over the "white-out".

In your response you acknowledge both your own as well as your staff's lack of experience with coordinating clinical investigations, so you discussed this violation in a research staff meeting. Proper documentation practices are essential to conduction of investigations. "White-out" should never be used to correct any source document. Discussion of this violation in a research staff meeting is not sufficient for it does not adequately address correcting the violative practice in the future and your procedure does not address using the most current IRB approved consent document. Please provide copies of policies and procedures, with expected completion dates that are being developed and implemented to ensure proper documentation of informed consent is completed.

In your response you note that you will obtain sponsor and IRB approval of any promotional materials used for an investigation. However, FDA's regulations at 21 CFR 812.7 prohibit sponsors, investigators, and all persons acting for or on behalf of sponsors or investigators from promoting investigational devices or representing that investigational devices are safe or effective for the purposes for which they are being investigated. Thus, there should not be any promotional materials pertaining to an investigational device.

Please note that eight of [REDACTED] subjects have been lost to follow-up for varying reasons. It is essential that discussion of the follow-up involved in a clinical trial is discussed and agreed to by the subject prior to enrollment. In addition, subject compliance should be considered when evaluating a subject for inclusion in an investigation. This investigational device is [REDACTED] and lack of follow-up is a safety concern.

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 Food, Drug, and Cosmetic Act and applicable federal regulations.

In your response, you note you and your staff are inexperienced. In review of the CV's of you and your study team there is no documented training which focuses on the conduct of investigational device studies. In order for you and your staff to better understand investigational study practices, you should consider attending and having your staff attend training sessions that focus on the operations of investigational studies.

We would like to remind you that as a clinical investigator, it is your responsibility to ensure that investigations that you participate in are conducted in accordance with applicable FDA regulations. You should refer to the regulations relevant to device studies, some of which were referenced below:

Investigational Device Exemptions - 21 CFR 812

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm>

Protection of Human Subjects – 21 CFR 50

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50&showFR=1>

Institutional Review Boards- 21 CFR 56

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=56&showFR=1>

Within fifteen (15) working days of receiving this letter, please provide written documentation of the additional 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. 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 C.F.R. 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. Send your response to: Attention: [REDACTED], Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, 9200 Corporate Boulevard, HFZ-311, Rockville, Maryland 20850.

A copy of this letter has been sent to FDA's Detroit District Office List address for the office. Please send a copy of your response to that office.

If you have any questions, please contact [REDACTED] by phone [REDACTED] or by email at [REDACTED].

Sincerely yours,



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