

WARNING LETTER

VIA FEDERAL EXPRESS

David M. Stern, M.D.
Dean, University of Cincinnati College of Medicine
231 Albert Sabin Way
Cincinnati, OH 45267

JAN 29 2007

Dear Dr. David Stern:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection conducted at University of Cincinnati Medical Center from March 7 through June 21, 2006, by an investigator from the FDA's Cincinnati District Office. The purpose of this inspection was to determine whether the University of Cincinnati's College of Medicine's activities as the sponsor of the clinical study,

complied with applicable federal regulations.
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 requests prompt corrective action to address the violations cited.

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.

The Investigational Device Exemption (IDE) application for submitted to the FDA on January 30, 1998, identified the University of Cincinnati College of Medicine as the sponsor of IDE a professor with tenure at the University of Cincinnati, is identified as the Principal Investigator and has been the point of contact for the FDA.

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 to for review and discussed the observations listed on the form with him. The deviations noted on the Form FDA 483, written responses, and our subsequent review of the inspection report are discussed below.

Failure to secure the investigator's compliance with the signed investigator agreement, the investigational plan, applicable FDA regulations, and any other conditions of approval imposed by the reviewing Institutional Review Board (IRB) or FDA. [21 CFR 812.46(a)]

A sponsor is responsible for securing investigator compliance with the signed agreement, the investigational plan, applicable FDA regulations, or any conditions of approval imposed by the reviewing IRB or FDA. If the investigator will not comply, it is the sponsor's responsibility to promptly secure compliance, or discontinue shipment of the device to the investigator and terminate the investor's participation in the investigation. You failed to secure investigator compliance with the investigation plan and applicable FDA regulations. Examples of this failure include but are not limited to:

- A) Diagnostic procedures/tests were not performed in accordance with the investigational plan. Some examples of this failure include but are not limited to:
- 1) The protocol requires Qualitative Outcome Assessments to be performed on [redacted]. These assessments were not performed for subject [redacted].
 - 2) The protocol requires [redacted] to be performed on [redacted] and [redacted] Subject [redacted] were not performed on [redacted] and [redacted]. In addition, Qualitative Outcome Assessments were not performed on [redacted] and [redacted]. The only documented assessment is [redacted] and this is incomplete in that there is no assessment for [redacted]. The protocol also requires [redacted] to be [redacted] prior to [redacted] of the device, on [redacted], and [redacted] for [redacted] were only obtained on [redacted].
 - 3) The primary [redacted] for [redacted] was not performed on subject [redacted].
 - 4) Subject [redacted] Qualitative Outcome Assessment on [redacted] and [redacted] for [redacted] percentage [redacted] were not performed. In addition, site [redacted] on [redacted] and [redacted] post [redacted] were not performed.
- B) [redacted] one of the approved clinical investigators, changed the protocol by changing the randomization process and the [redacted] procedure without sponsor approval, and [redacted].
- C) Case histories are incomplete in that they lack documentation and reporting of unanticipated adverse device events. Examples of this failure include but are not limited to the following:
- 1) On [redacted] subject [redacted] had positive cultures for [redacted] of her [redacted] which resulted in clinical sepsis. She was treated with triple antibiotic therapy of [redacted] and [redacted]. This event was not recorded on the adverse event case report forms (CRF) and there was no documentation of reporting this event to the sponsor, IRB, and FDA.

- 2) Subject developed an infection of the left posterior positive with and Staph species on Infection of the is not identified in the protocol as an anticipated event therefore, it was an unanticipated adverse device effect and required reporting to the reviewing IRB and sponsor. There is no documentation of this event being reported to the sponsor, IRB, and FDA.
- 3) Subject Qualitative Outcome Assessment CRF noted of for both and however there is no documentation of reporting of this event to the sponsor, IRB, and FDA.
- 4) Subject Qualitative Outcome Assessment CRF's dated , and identified as This is an unanticipated adverse device effect; however, there is no documentation of reporting of these events to the sponsor, IRB, and FDA.

In response, he stated the current study contains multiple endpoints that are not relevant to the demonstration of safety and efficacy of the investigational device and that therefore, he is revising the study protocol. Please submit the proposed revised protocol to the FDA. Revising the protocol should assist with improving protocol compliance; however, the response is inadequate in that it did not include a plan to ensure clinical investigators participating in the study will adhere to the investigational plan and FDA regulations in the future. Please provide copies of policies and procedures, with expected completion dates, that are being developed and implemented to ensure that all clinical investigators participating in the study adhere to the signed agreement, the investigational plan, applicable federal regulations, and any other conditions of approval imposed by the reviewing IRB or FDA. In addition, please provide copies of policies and procedures, with expected completion dates, that are being developed and implemented to manage investigators from whom you are unable to secure compliance.

In accordance with 21 CFR 812.140(a)(3)(ii), a participating investigator shall maintain records of each subject's case history and exposure to the device. These records shall include documentation of all relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests. In addition, in accordance with 21 CFR 812.150(b)(1), a sponsor shall prepare and submit to FDA and all reviewing IRBs complete, accurate, and timely reports of evaluations of unanticipated adverse effects within ten working days after the sponsor receives notice of the unanticipated adverse device effect. Unanticipated adverse device effects include device failure such as regrafting.

In response, he stated he will report unanticipated events to FDA and the sponsor. He further stated that anticipated adverse events that are described in the study protocol are not reportable. Because the protocol does not define what events are considered anticipated and it does not include a plan to evaluate and report unanticipated adverse device effects, please clarify what events are anticipated. Please submit a summary and description of all unanticipated adverse device effects. In

addition, please provide copies of policies and procedures, with expected completion dates that are being developed and implemented to ensure all unanticipated adverse device effects are evaluated and reported to the FDA and reviewing IRBs.

Failure to ensure adequate monitoring of the investigation and failure to include written procedures for monitoring the investigation in the investigational plan. [21 CFR 812.40, 21 CFR 812.25(e)]

Sponsors are responsible for ensuring proper monitoring of the investigation. An investigational plan shall include written procedures for monitoring of the investigation and include the name and address of monitors. At the time of the inspection, there were no written procedures for monitoring the investigational device study and there was no documentation of monitoring of the investigation.

In response, he submitted a draft investigative monitoring plan dated September 1, 2006. The plan states that the monitoring will be performed by the associate director of clinical trials or an appointed designee. In accordance with 21 CFR 812.43(d), a sponsor shall select monitors qualified by training and experience to monitor the investigation. Therefore, this plan is inadequate, in that it does not contain a process for assurance of selection of qualified monitors. Please provide documentation of the qualification of the monitors.

Failure to prepare and submit progress reports at regular intervals and at least yearly to FDA and reviewing IRBs. [21 CFR 812.150(b)(5)]

At regular intervals, and at least yearly, a sponsor shall submit progress reports to all reviewing IRB's. In this case, because it involves a significant risk device, a sponsor shall also submit progress reports to FDA. Examples of failure to submit progress reports to the FDA include but are not limited to:

The annual reports submitted to FDA are dated: June 1, 1999, July 14, 2000, November 16, 2001, January 14, 2003, September 24, 2004, and January 2, 2006. Accordingly, progress reports were not submitted to the agency at least yearly.

Please provide copies of policies and procedures with expected completion dates that are being developed and implemented to ensure progress reports are submitted to the FDA and reviewing IRBs at regular intervals and at least yearly.

Failure to label the device as investigational. [21 CFR 812.5(a)]

An investigational device or its immediate package shall bear a label with the following information: the name and place of business of the manufacturer, packer, or distributor, the quantity of the contents, and the following statement "CAUTION-Investigational device Limited by Federal (or United States) law to investigational use." The other label or labeling shall describe all relevant contraindication, hazards, adverse effects, interfering substances or devices, warnings, and precautions.

The investigational devices, did not contain the proper labeling. Examples of information not included are:

- The name and place of business of manufacturer, packer, or distributor, and
- The statement "CAUTION-Investigational device Limited by Federal (or United States) law to investigational use."

In response he stated a label that includes the information required by federal law will be used in the future and he submitted an example of a label containing the name and place of business of manufacturer, and the statement "CAUTION-Investigational device Limited by Federal (or United States) law to investigation use." This label and labeling is incomplete, and thus inadequate, in that the label or labeling shall also describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions. Please provide a copy of the label or labeling that provides this information.

Failure to maintain accurate, complete and current device shipment and disposition records. [21 CFR 812.140(b)(2)]

A sponsor shall maintain accurate, complete, and current records relating to shipment and disposition of devices. You failed to maintain records of shipment and disposition of investigational devices in accordance with 21 CFR 812.140(b)(2).

In response, he stated all the investigational devices in the study are labeled with a lot number. The process takes a minimum of and normally are made at this time. Each of is until they are ready for the devices are in a and then the subject. Once the are ready, they are kept and complete records of investigational device shipments and disposition were not maintained. There was some documentation in subject files relating to the lot numbers and ; however, this is incomplete in that it does not contain: name and address of the consignees, date of shipment, lot numbers of devices returned to the sponsor, repaired, or disposed of in any other manner by the investigators or anyone else, and the reasons for and method of disposal. response is thus inadequate. Please provide copies of policies and procedures with expected completion dates that are being developed and implemented to ensure all the aforementioned device shipment and disposition information is maintained.

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 study sponsor to ensure compliance with the Act and applicable regulations.

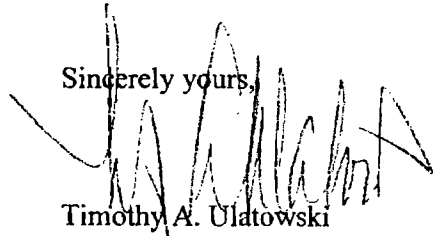
Within fifteen (15) working days of receiving this letter, please provide written documentation of the actions you have taken or will take to correct these violations and prevent the recurrence of similar violations in current or future studies for which you are

the study sponsor. Any submitted corrective action plan should include projected completion dates for each action to be accomplished. Failure to respond to this letter and take appropriate corrective action could result in withdrawal of your IDE under 21 CFR 812.30(b). Send your response to: Attention: Doreen Kezer, Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, 9200 Corporate Boulevard, HFZ-310, Rockville, Maryland 20850.

A copy of this letter has been sent to Cincinnati District Office, 6751 Steger Drive, Cincinnati, OH, 45237-3097. Please also send a copy of your response to that office.

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

Sincerely yours,



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

cc.

Jane Henney, M.D.
Senior Vice President and Provost for Health Affairs
HPB 250
P.O. Box 670663
Cincinnati, OH 45267

Sandra Degen, Ph.D
Vice President for Research, Ofc of HPB
P.O Box 670663
Cincinnati, OH 45267

University of Cincinnati Medical Center Institutional Review Board
Eden and Bethesda Avenues
PO Box 670567
Cincinnati, OH 45267-0567