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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

NOV 13 2008

WARNING LETTER

VIA FEDERAL EXPRESS

Ali R. Rezai, M.D.
Center for Neurological Restoration
Cleveland Clinic Foundation, S-31
9500 Euclid Avenue
Cleveland, OH 44195

Dear Dr. Rezai:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection conducted at your facility from July 22 through August 29, 2008, by investigators from the FDA Cincinnati District Office. The purpose of this inspection was to determine whether your activities and procedures related to your participation as both sponsor and clinical investigator in the clinical studies entitled: (b) (4) [redacted], complied with applicable federal regulations. These (b) (4) studies involved the use of the (b) (4) [redacted] with (b) (4) [redacted]. The (b) (4) [redacted] 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 written response dated September 2, 2008.

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 serious violations of Title 21, Code of Federal Regulations (21 CFR) Part 812 -- Investigational Device Exemption. At the close of the inspection, the FDA investigators presented an inspectional observations Form FDA 483 for your review and discussed the observations listed on the form with you. The deviations noted on the FDA 483, our subsequent review of the inspection report and your response are discussed below:

Citations related to your role and responsibilities as the sponsor of the (b) (4), and (b) (4) clinical studies:

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

A sponsor is responsible for preparing and submitting complete and accurate progress reports at regular intervals, and at least yearly, to all reviewing IRBs and, in the case of a significant risk device (as is your device), the sponsor shall also submit progress reports to the FDA. Examples of your failures include, but are not limited to, the following:

- You did not submit progress reports for (b) (4) for (b) (4).
- You did not submit a progress report for (b) (4) for (b) (4).
- You did not submit progress reports for (b) (4) for (b) (4).

Your response states that the study (b) (4) is now closed and final progress reports were submitted to both the FDA and IRB in (b) (4), and that in order to prevent this violation in the future you have established a flow chart that will be reviewed at your monthly status update meetings. Your response for all (b) (4) studies references Appendices IX, and X, however, neither of these provide a corrective and preventive plan.

Your response regarding studies (b) (4) also references Appendices II, IX, and X. Your response is inadequate because it is unclear how these reflect any corrective action to address this deficiency. Please provide your corrective and preventive actions regarding the timely submission of progress reports.

We acknowledge your response that for study (b) (4), you have a revised weekly status reporting which is intended to eliminate the failure to submit progress reports and that you will submit the (b) (4) progress on time for this study, and for study (b) (4)

2. Failure to obtain from each participating investigator a signed agreement that includes sufficient accurate financial disclosure information to allow the sponsor to submit a complete and accurate certification or disclosure statement [21 CFR 812.43(c)(5)].

A sponsor is responsible for obtaining a signed agreement from each investigator that includes sufficient accurate financial disclosure information to allow the sponsor to submit a complete and accurate certification or disclosure statement. You failed to obtain a signed agreement that includes sufficient accurate financial disclosure information from all persons listed as investigators:

(b) (4)

You failed to obtain investigator agreements from six eight investigators who participated in the study.

You did not sign a financial agreement until (b) (4), although this study began in (b) (4)

(b) (4)

In addition to you, there were six investigators who participated in this study. You failed to obtain investigator agreements from any of the investigators who participated in this study.

(b) (4)

You obtained financial disclosure for only two of the 15 investigators involved in this study.

Your response to this deficiencies states that future IDE submissions will use a checklist to assure completion of all elements necessary for a complete protocol submission, and references Appendix XII. Your response is inadequate, in that no such checklist was provided, and the referenced appendix, entitled "Required Sponsor Reports to a FDA Accepted IDE," does not contain any reference to investigator agreements or financial disclosure information.

Citations related to your role and responsibilities as a clinical investigator (b) (4) clinical studies:

3. Failure to conduct the investigation according to the signed agreement, the investigational plan, and applicable FDA regulations. [21 CFR 812.100 and 21 CFR 812.110(b)]

An investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan, and applicable FDA regulations, for protecting the rights, safety, and welfare of subjects under the investigator's care, and for the control of devices under investigation. You failed to conduct the investigation in accordance with the investigational plan in each of the three studies inspected. Examples of your failure include, but are not limited to, the following:

(b) (4)

- The protocol required that subjects be (b) (4) with (b) (4) however, you deviated from the protocol in that Subject (b) (4) was (b) (4) with only (b) (4) device.

- The protocol required that (b) (4) post-surgical functional (b) (4) be performed; however, there is no documentation of a (b) (4) for any of the (b) (4) subjects enrolled in this study.

Your response states that these deviations were reported to the IRB and the FDA in September, 2008. Your corrective action references steering committee weekly meetings which will include review of potential deviations and recommendations for protocol amendments. As stated above, you may delegate some of your clinical investigator duties to others, but you remain responsible for the conduct of the studies. Your response is inadequate, in that none of the appendices you have referenced describes how protocol deviations will be prevented.

(b) (4)

- The protocol required that (b) (4) be (b) (4) You deviated from the protocol in that you (b) (4) a different (b) (4) in at least (b) (4) subjects:

  A (b) (4) was (b) (4) into subject (b) (4) on (b) (4) and into subject (b) (4) on (b) (4)

Your response states that in the future, decision regarding protocol deviations will be reviewed by the steering committee and appropriate actions taken based on the decisions made by this committee. Your response is inadequate, in that you have not provided a corrective action as to how this deviation will be prevented in the future. Please note that the steering committee can not assume the responsibilities of the sponsor of the clinical investigators. In addition, your reference to Appendix XI is a Progress Report Flow Chart which does not address this violation.

4. Failure to maintain accurate, complete, and current case histories. [21 CFR 812.140(a)(3)].

An investigator is responsible for maintaining accurate, complete, and current records of each subject's case history and exposure to the device, which encompasses the case report forms (CRF) and supporting data. In addition, case histories shall contain all relevant observations, including records concerning adverse device effects. In at least (b) (4) studies, you failed to maintain accurate, complete, and current records of subject's case histories as required. Examples of these failures include, but are not limited to, the following:

(b) (4)

The protocol preoperative studies include the (b) (4), the (b) (4) the (b) (4) and the (b) (4) are pre surgical baseline follow-up test batteries to be performed by a psychiatrist or specially trained interviewer. Additional studies include the (b) (4)

(b)(4) For all (b)(4) of the subjects enrolled in this study, records were incomplete, as follows:

For Subject (b)(4) Subject identification (ID), the examiner's initials, and the date of the visit are missing.

For Subject (b)(4) Examiner's initials missing and subject ID are missing.

For Subject (b)(4) Subject ID, dates, and examiner's initials are missing.

For Subject (b)(4) Subject ID, dates, and examiner's initials are missing.

For Subject (b)(4): Subject ID, dates, and, examiner's initials are missing.

(b)(4)

The protocol states that clinician rated scales will be performed by a psychiatrist or specially trained interviewer. The records for subject (b)(4) are incomplete in that pages are missing subject ID, dates, and examiner's initials.

Your response states that you will engage the services of a Contract Research Organization (CRO) to perform a (b)(4) source verification of the subjects (b)(4) Upon completion of this audit, you state that you will develop a corrective action plan which will include training of the study team and the implementation of a monitoring plan prior to enrolling into a study. Your response also references to Appendices I and V as part of the plan. Although Appendix I does include some SOPs, none of them appear to address the issue of records, and several only reference 21 Code of Federal Regulations (CFR) 312, which refer to drug regulations rather than device regulations (21 CFR 812) which apply to the studies named above. In addition, our review of the SOP included as Appendix V noted that it does not address subject case histories, source documents, or case report forms. Your response is inadequate in that it does not provide substantive corrective actions or any preventive actions to avoid recurrence of the violations (i.e., development of standard operating procedures (SOPs), policies, or other means that would ensure compliance with the device regulations.

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 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. 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 at 6751 Steger Drive, Cincinnati, OH, 45237. Please send a copy of your response to that office.

If you have any questions, please contact Doreen Kezer, (240) 276-0125.

Sincerely yours,

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