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WARNING LETTER

VIA FEDERAL EXPRESS

Sarah H. Lisanby, M.D.
1051 Riverside Drive Unit
Room 5100
New York, NY 10032

OCT 6 2008

Dear Dr. Lisanby:

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 May 19, 2008 to June 9, 2008, by an investigator from the FDA New York District Office and a Compliance Officer from the FDA Center for Devices and Radiological Health, Rockville, Maryland. The purpose of this inspection was to determine whether your activities as a sponsor and investigator of "(b)(4) for the (b)(4) study utilizing the (b)(4) device, (b)(4) and (b)(4) study utilizing the (b)(4) (b)(4) complied with applicable federal regulations. The (b)(4) and the (b)(4) are devices, 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 requests prompt corrective actions to address the violations cited and discusses your written response, dated June 23, 2008, to the noted violations.

The inspection was conducted under a program designed to ensure that data and information contained in requests for 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 Exemptions, and Section 520(g) (21 U.S.C. 360j(g)) of the Act. 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, (b)(6) and (b)(6) and (b)(6). The deviations noted on the form FDA 483, your written response, and our subsequent review of the inspection report are discussed below:

Failure to obtain FDA approval prior to implementing a change in the investigational plan [21 CFR 812.35(a)(1)].

It is your responsibility to obtain FDA approval (with certain exceptions) prior to implementing any change to the investigational plan (21 CFR 812.35(a)(1)). You failed to obtain FDA approval for an increase in the upper age limit from 35 to 75 years of age. An example of your failure includes, but is not limited to, the following:

- On June 13, 2003, the FDA approved your supplemental application for a change in the investigational plan to increase the upper age limit from 30 to 35 years of age related to your protocol for (b)(4). Since 2003, FDA has not approved any other age increases. In March 2006, you requested IRB approval to increase the upper age from 35 to 75 years of age and received approval on June 6, 2006. You did not submit a supplemental application or obtain FDA approval for this change in the investigational plan.

Failure to ensure proper monitoring of the investigation [21 CFR 812.40].

As a sponsor, you are responsible for ensuring proper monitoring of the investigation. Your monitoring was inadequate because you failed to monitor in accordance with your written monitoring procedure. Examples of this failure include, but are not limited to, the following:

- For (b)(4), the Study Monitoring Manual states that prior to starting the clinical trials, you will visit the (b)(4).
(b)(4)
(b)(4) However, during the FDA inspection you could not provide documentation of monitoring or monitoring reports that indicate the completion of any of the monitoring manual requirements at (b)(4).

As a consequence of your failure to monitor, you did not identify deficiencies at your clinical site. For example, (b)(4), a clinical investigator participating in the study, did not adhere to the protocol requirements and eight subjects did not complete the required (b)(4) and he did not maintain device receipt, use, and disposition records, which were required by the protocol.

Your response states that the monitoring conducted at (b)(4) was recorded in the Study Monitoring Log, and that both (b)(4) were complying with study procedures and continuing to fulfill their investigator responsibilities. You indicate in your corrective action plan that you will revise the monitoring plan to address this violation. Your written response is inadequate in that you failed to provide copies of policies, procedures,

and training plans that are being developed and implemented to prevent the recurrence of these violations in future clinical studies.

Failure to obtain from each participating investigator a signed agreement that includes a curriculum vitae and sufficient accurate financial disclosure information [21 CFR 812.43(c)(1) and 21 CFR 812.43(c)(5)].

A sponsor shall obtain from each participating investigator a signed agreement (21 CFR 812.43(c)). The agreement must include a curriculum vitae (CV) and sufficient accurate financial disclosure information (21 CFR 812.43(c)(1) and 21 CFR 812.43(c)(5)). You failed to obtain a signed agreement that includes a CV or sufficient accurate financial disclosure information from each participating investigator. Examples of this failure include, but are not limited to, the following:

- There was not a signed investigator agreement that included a CV for (b)(6)
- There were not signed investigator agreements that included financial disclosure information for (b)(6) and (b)(6)

In your response, you indicate that you now understand that you need to prospectively collect investigator agreements that include CVs and financial disclosure information from all investigators, and that you have changed your study monitoring standard operating procedure (SOP) to address this violation. Your response is inadequate in that you have not provided a copy of the policy, CVs and financial disclosure information for all investigators, and a copy of the revised monitoring SOP.

Failure to ensure an investigation is conducted in accordance with the signed agreement, the investigational plan, and applicable FDA regulations, for protecting the rights, safety, and welfare of subjects under the investigator's care [21 CFR 812.100 and 21 CFR 812.110(b)].

As a clinical investigator, you failed to conduct the investigation in accordance with the investigational plan for (b)(4). Subjects who did not meet the eligibility criteria were enrolled in the study. Examples of your failure include, but are not limited to, the following:

- The protocol states that subjects with a current or past history of (b)(4) (b)(4) should be excluded from the study; however, Subject (b)(6) and received the first study (b)(4) on (b)(6)
- The protocol states that all subjects will receive routine laboratory work including (b)(4). Subject (b)(6) (b)(4) (b)(4) test results were not obtained prior to study treatment to determine if

the subject met the exclusion criteria. The subject received the first study (b)(4) on (b)(6), and the (b)(4) test results were never obtained.

Your response indicates that both of the subjects met the inclusion criteria. Your response is inadequate in that you did not provide documentation of the subjects' eligibility. Please provide documentation of both subjects' eligibility, as well as copies of policies and procedures that are being developed to ensure all study subjects meet eligibility criteria prior to being enrolled in the study.

Failure to maintain accurate, complete, and current records of receipt, use, or disposition of a device and records of each subject's case history and exposure to the device [21 CFR 812.140(a)(2)(i) and 21 CFR 812.140(a)(3)].

- As a clinical investigator, you are responsible for maintaining accurate, complete, and current records of study-related matters, including receipt and use of a device that relate to the type and quantity, dates of receipt, batch number or code mark (21 CFR 812.140(a)(2)(i)). You are also required to maintain records of each subject's case history and exposure to the device (21 CFR 812.140(a)(3)). Examples of your failure include, but are not limited to, the following:
 - Your records indicated that subjects (b)(6) and (b)(6) (b)(4) with device #(b)(4) during the period of (b)(6) through (b)(6). However, the device control records indicate that the device was being repaired during this time period and another device (#(b)(4)) was being used in its place.

Your response notes that device #(b)(4) was sent for repair on September 11, 2002 and returned on September 18, 2002, and that you found discrepancies in your device control records. You state that you have revised your procedures related to device control. Your response is inadequate in that you did not provide copies of the revised written procedures, implementation dates, and a staff training log.

- For (b)(4), there were two devices (#(b)(4) and #(b)(4) located at (b)(4). The records do not indicate which device was utilized on thirty one subjects.

According to your letter, the (b)(4) and (b)(4) did not have a data entry field for the device serial number and you had *implicit* knowledge of which device was used for each subject. As required by the regulations, you must maintain each subject's case history and exposure to the study device (21 CFR 812.140(a)(3)). Your response is inadequate in that you did not provide documentation to show which device was used to administer the study treatment and the location of treatment.

As an investigator, failure to prepare and submit progress reports to the institutional review board (IRB) at regular intervals, but in no event less often than yearly [21 CFR 812.150(a)(3)]. As a sponsor, failure to submit progress reports at regular intervals, and at least yearly, to the IRB [21 CFR 812.150(b)(5)].

- For (b)(4) [redacted], as an investigator, you failed to submit progress reports to the IRB at regular intervals, but in no event less often than yearly, as required by 812.150(a)(3). As stated above, the study was approved by the IRB on March 4, 2003, and you failed to submit a progress report to the IRB by March 4, 2004. Additionally, the study was again approved by the IRB on March 4, 2006, and you failed to submit a progress report to the IRB by March 4, 2007.
- For (b)(4) [redacted] as a sponsor, you failed to submit progress reports to the FDA in 2004, 2005, and 2007. Your study involves a significant risk device; therefore, you, as a sponsor, must submit progress reports to the FDA, as required by 21 CFR 812.150(b)(5). Additionally, you failed to submit progress reports to the IRB at regular intervals, and at least yearly, as required by 21 CFR 812.150(b)(5). The study was approved by the IRB on March 4, 2003, and you failed to submit a progress report to the IRB by March 4, 2004, one year after the study was approved by the IRB. Additionally, the study was again approved by the IRB on March 4, 2006, and you failed to submit a progress report to the IRB by March 4, 2007, one year after the study was approved by the IRB.

Please submit copies of policies, procedures, and training with expected completion dates that are being developed to ensure the above deviations do not recur in current and future studies. Also, provide documentation of the procedures that will be implemented to ensure FDA and IRB approval prior to initiation or changes to any studies, and include a copy of the revised TMS Administration Log/Datasheets with information related to the study device used.

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 sponsor/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 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 study sponsor/clinical investigator. Any submitted corrective action plan must include projected completion dates for each action to be accomplished.

In addition, please provide a complete list of all clinical trials in which you have sponsored or 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. FDA could initiate disqualification proceedings against you in accordance with 21 CFR 812.119.

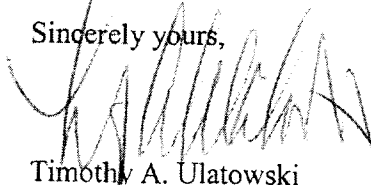
You will find information to assist you in understanding your responsibilities and planning your corrective actions in the FDA Information Sheets Guidance for Institutional Review Boards and Clinical Investigators, which can be found at <http://www.fda.gov/oc/ohrt/irbs/>. Any submitted corrective action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

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: Linda D. Godfrey, Chief, 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 New York District Office at 158-15 Liberty Avenue, Jamaica, New York 11433. Please send a copy of your response to that office.

If you have any questions, please contact Linda D. Godfrey, by telephone at (240) 276-0125, or by e-mail at Linda.Godfrey@fda.hhs.gov.

Sincerely yours,



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