Inspections, Compliance, Enforcement, and Criminal Investigations

Richard E. Ringel, M.D.

hhsbluebirdDepartment of Health and Human Services

Public Health Service
Food and Drug
Administration

9200 Corporate Boulevard

Rockville, Maryland 20850

WARNING LETTER

May 20, 2009

VIA FEDERAL EXPRESS

Richard E. Ringel, M.D.
600 North Wolfe Street
Brady 516
Baltimore, Maryland 21287

Dear Dr. Ringel:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection conducted at your facility from January 21, 2009 to February 3, 2009, by an investigator from the FDA Baltimore 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 study of the **(b)(4)** complied with applicable federal regulations. **(b)(4)** 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 and discusses your written response to the noted violations.

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 Exemptions. 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, and with **(b)(6)** The deviations noted on the FDA 483, your written response, and our subsequent review of the inspection report are discussed below:

Citations related to your role and responsibilities as the sponsor of the clinical study

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

Sponsors are responsible for ensuring proper monitoring of an investigation. The investigational plan states that you as the Principal Investigator will be responsible for coordination of all aspects of the investigation including monitoring the study. **(b)(4)** subjects have been enrolled across **(b)(4)** investigational sites beginning February 8, 2008. Examples of your failures include, but are not limited to, the following:

1. You did not assure that the Data Coordinating Center (DCC) monitored each of the investigative sites as stated per protocol.
2. You did not assure, according to the protocol and the Monitoring Plan dated August 13, 2008, that data collection was overseen by an independent study monitor, nor that any monitoring of the study was conducted at any time.

In your response dated February 10,,2009, you acknowledged the lack of monitoring and stated that the monitoring will be performed by the **(b)(4).** You submitted the monitoring plan and included a copy of a COAST participating site monitoring schedule.

Your response is inadequate in that your plan does not provide for on-going oversight of the clinical study. The monitoring schedule should not be a one-time event but should be an on-going program performed with the frequency necessary to ensure that clinical investigators are complying with the signed agreement, the investigational plan, FDA regulations, and any conditions of approval imposed by FDA or the reviewing IRB. Although you may delegate the task of monitoring, as the sponsor you are ultimately responsible for ensuring proper monitoring of the investigation.

Failure to obtain a signed agreement that included a statement of each participating investigator's commitment to supervise all testing of the device involving human subjects and failure to obtain sufficient accurate financial disclosure information from each participating investigator. [21 CFR 812.43(c)(4)(ii) and (c)(5)]

The sponsor is responsible for obtaining a signed agreement from each investigator that includes a statement of the investigator's commitment to supervise all testing of the device involving human subjects. A sponsor is also required to obtain financial disclosure information from each clinical investigator. This financial disclosure information should allow the sponsor to submit a complete and accurate certification or disclosure of a clinical investigator's financial interests and arrangements. This statement should include a commitment to promptly update financial disclosure information if any relevant changes occur during the investigation and for one year following completion of the study. Examples of your failure include, but are not limited to the following:

- You failed to obtain signed investigator agreements from all **(b)(4)** participating investigators that included an agreement that the investigator will supervise all testing of the device involving human subjects.
- You failed to obtain financial disclosure information from the following eleven clinical investigators.

(b)(5)

In your response you acknowledge that the above-mentioned statement of commitment and financial disclosure information were not obtained as required. You have included a draft of an additional investigator's agreement in which the statement of commitment and financial disclosure information language are included.

Please provide copies of the final signed investigator agreements and the financial disclosure information submitted by all investigators. Please include copies of corrective actions you are developing and implementing to ensure that this deficiency does not reoccur in this and future studies.

Failure to prepare and submit current investigator list to FDA at 6-month intervals. [21 CFR 812.150(b)(4)]

A sponsor is responsible for preparing and submitting to FDA, at 6-month intervals, a current list of the names and addresses of all investigators participating in the investigation. You have failed to submit a current clinical investigator list to FDA as required at 6-month intervals since receiving FDA approval on August 3, 2007.

In your response you acknowledge that a current list of the names and addresses of all investigators has not been submitted as required. You included a draft copy of a list of the sites and their principal as well as sub-investigators. You stated that this list will be sent to Center for Devices and Radiological Health (CDRH) as a supplement to the IDE protocol and you will continue to provide this information on a semi-annual basis. Your response is adequate.

Citations related to your role and responsibilities as the clinical investigator of the study

Failure to conduct the investigation according to the signed agreement, the investigational plan, applicable FDA regulations, and any conditions of approval imposed by FDA or the reviewing IRB. [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, applicable FDA

regulations, and any conditions of approval imposed by FDA regulations, and any conditions of approval imposed by FDA or the reviewing IRB. Examples of your failure include, but are not limited to, the following:

The investigational plan states that "the principal investigator will be responsible for coordination of all aspects of the investigation." One of the aspects of the investigation includes the data safety monitoring board (DSMB). The protocol1 states that the DSMB will meet **(b)(5)** Although **(b)(4)** subjects were enrolled since February 8, 2008, no DSMB meetings were held since enrollment.

In your response you acknowledge that you failed to follow the investigational plan concerning DSMB meetings and state that you have changed the protocol to read, **(b)(5)** Please provide copies of minutes documenting any DSMB meetings to date. Please also provide copies of corrective actions you have implemented or plan to implement to ensure that, in future studies, the protocol will be followed.

The protocol states that **(b)(5)** on both **(b)(6)** but was not implanted with the device until **(b)(6)** which is a deviation from the protocol.

In your response you acknowledge this protocol deviation and state that, as the sponsor, you reported this change to the investigational plan in your annual report to FDA [21 CFR 812.35(a)(4)]. However, your response does not provide corrective or preventative actions to avoid recurrence of similar protocol violations in this study. Please also provide copies of all corrective actions you have developed to ensure that, in future studies, the protocol will be followed.

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 and clinical investigator to ensure compliance with the Act and applicable regulations.

Regarding the financial disclosure referenced above, you can reference the following internet site for further information:
http://www.fda.gov/oc/gcp/preambles/63fr5233.html

A sample Form FDA 3455 Financial Disclosure form for Clinical Investigators can be found at the following site:
http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3455.pdf

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. 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: Levering Keely, 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 Baltimore District Office, 6000 Metro Drive, Suite 101, Baltimore, Maryland 21215. Please send a copy of your response to that office.

If you have any questions, please contact Levering Keely, 301-796-5663, or email: Levering.Keely@fda.hhs.gov.

Sincerely yours,

/S/

Timothy A. Ulatowski

Director

Office of Compliance

Center or Devices and

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Cc:
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1- The protocol is part of the investigational plan. 21 CFR 812.25(b).