Inspections, Compliance, Enforcement, and Criminal Investigations

Perez-Cruet, Miguelangelo J., M.D., M.S. 3/2/10

Department of Health and Human Services

Public Health Service
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

WARNING LETTER

VIA FEDERAL EXPRESS

MAR 2 2010

Miguelangelo J. Perez-Cruet, M.D., M.S.
3577 West 13 Mile Road, Suite 206
Royal Oak, MI 48073

Dear Dr. Perez-Cruet:

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 September 14, 2009 to December 2, 2009 by an investigator from the FDA Detroit District Office. The purpose of this inspection was to determine whether activities and procedures related to your participation in the clinical studies **(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 dated December 6, 2009, 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 several violations of Title 21, Code of Federa1 Regulations (21 CFR) 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 deviations noted on the Form FDA 483, your written response, and our subsequent review of the inspection report are discussed below:

1. Failure to ensure that informed consent is obtained in accordance with 21 CFR Part 50. [21 CFR 50.20, 21 CFR 50.27(a), and 21 CFR 812.100]

An investigator is responsible for obtaining informed consent from each subject using an Institutional Review

Board (IRB) approved version of the informed consent document prior to involving the subjects in the clinical investigation. You failed to ensure that informed consent was obtained from subjects in accordance with the federal regulations. Examples of this failure include but are not limited to the following:

Three subjects (subjects **(b)(4)** and **(b)(4)**) in the **(b)(4)** study were given the **(b)(4)** study informed consent form which differs in describing the follow-up times and whether all subjects would be implanted with the investigational device. Subject **(b)(4)** signed the informed consent form which indicated that all subjects would received the investigational device; however, the subject was implanted with the control device.

Your response is inadequate in that it does not describe your corrective and preventive actions for failing to use the correct versions of informed consent. Your response states that you are being educated on clinical trials and have been given guidance by the Sponsor. Please explain how you have corrected these past failures and provide a mechanism for preventing any recurrence.

2. Failure to ensure an investigation is conducted according to the signed agreement, the investigational plan, applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA. (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. Examples of this failure include but are not limited to the following:

(b)(4) Study:

• Seven subjects out of 25 were enrolled into the study who met the exclusion criteria of "**(b)(4)**" Specifically,

o Subject **(b)(4)** has **(b)(4)**.
o Subject **(b)(4)** has a **(b)(4)**.
o Subject **(b)(4)** has **(b)(4)**.
Subject **(b)(4)** has **(b)(4)**

• The study protocol, section 7.2, requires the clinical investigator, or designate, to report major complications including anticipated and unanticipated events no later than 5 days after and preferably within 24 hours of the occurrence. Two subjects experienced major complications which were not reported:

o Subject **(b)(4)**
o Subject **(b)(4)**

(b)(4) Study:

• For 10 subjects out of 26, there were medications missing from the "Concomitant medications Form." Protocol section 2.3.7.3 states the following: "Information regarding all prescription pain medications, narcotic and non-narcotic that the subject is currently taking will be recorded. The information will include the medication name, and the indication for which the medication is taken." Some examples of the medications you prescribed but did not record appropriately on the Concomitant Medications Form are the following:

o Subject **(b)(4)**:

o Subject **(b)(4)**:
o Subject **(b)(4)**:
o Subject **(b)(4)** and **(b)(4)**:
o Subject **(b)(4)**:

• For 10 subjects out of 26, completed Case Report Forms (CRFs), logs, and other subject specific forms were signed by the study coordinator rather than the clinical investigator. The protocol, section 5.3.1, *Investigator Records*, states that the investigator is responsible for the preparation (review and signature) and retention of the subjects' records.

o Subjects **(b)(4)** had their Follow-Up evaluation form signed by the Clinical Trial Study Coordinator.
o Subjects **(b)(4)** and **(b)(4)** had their Pre-Operative evaluation form signed by the Clinical Trial Study Coordinator.
o Subjects **(b)(4)** and **(b)(4)** had their Eligibility and Pre-Operative evaluation forms signed by the Clinical Trial Study Coordinator.

Your response is inadequate in that it does not describe your corrective and preventive actions for enrolling ineligible subjects, failing to report AEs in the time required, failure to report all the subjects' concomitant medications and ensuring the clinical investigator, rather than the study coordinator, signs completed CRFs, logs, and other subject specific forms. Your response states that you are being educated on clinical trials and have been given guidance by the Sponsor. Please explain how you will correct these past protocol deviations and provide mechanisms for preventing their recurrence.

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 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 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 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. Send your response to: Attention: Anne Hawthorn, Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, 10903 New Hampshire Avenue, WO66-3504, Silver Spring, Maryland, 20993-0002.

A copy of this letter has been sent to the Detroit District Office: 300 River Place Suite #5900 Detroit, MI 48207. Please send a copy of your response to that office.

The Division of Bioresearch Monitoring has developed introductory training modules in FDA regulated device clinical research practices, which are available on the FDA website. The modules are for persons involved in FDA regulated device clinical research activities. These modules are located at the following website address: http://www.fda.gov/Training/CDRHLearn/ucm162015.htm

If you have any questions, please contact: Anne Hawthorn, at 301 796-6561 or anne.hawthorn@fda.hhs.gov.

Sincerely yours,
/S/
Michael E. Marcarelli, Pharm. D., MS

Director, Division of Bioresearch Monitoring
Office of Compliance
Center for Devices and
Radiological Health

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