Inspections, Compliance, Enforcement, and Criminal Investigations

Potter, Daniel A., M.D.

Department of Health and Human Services

Public Health Service
Food and Drug
Administration
10903 New Hampshire
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WARNING LETTER

VIA FEDERAL EXPRESS

NOV 2 2009

Daniel A. Potter, M.D.
Huntington Reproductive Center Medical Group
23961 Calle de Magdalena, Suite #503
Laguna Hills, CA 92653

Dear Dr. Potter:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection conducted at your clinical site and to request a prompt reply.

During the period from June 16 to June 30, 2009 an investigator from the FDA Los Angeles District Office conducted an inspection of your site. The purpose of this inspection was to determine whether activities and procedures related to your participation in the clinical study "The Safety and effectiveness of the **(b)(4)** Premarket Approval (PMA) application **(b)(4)** Investigational Device Exemption (IDE) **(b)(4)** complied with applicable federal regulations. The **(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). The letter also requests prompt corrective action to address the violations cited and discusses your written response and the response written by David Karabinus, PhD, HCLD, on your behalf dated July 15, 2009, 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 several violations of Title 21 Code of Federal Regulations (21 CFR) Part 50 - Protection of Human Subjects and Part 812 - Investigational Device Exemptions. At the close of the inspection, the FDA investigator presented an inspectional observations form FDA 483 for review and discussed the observations listed on the form with Ms. Kelly D. Hoffman **(b)(4)** Clinical Coordinator, acting in your absence), Ms. Nachet Harris **(b)(4)** Clinical Coordinator), and Melissa Terra (HRC Marketing representative). The deviations noted on the FDA 483, the 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 50.25, 21 CFR 50.27(a)].

As a clinical investigator, you are responsible for ensuring that informed consent is obtained in accordance with 21 CFR Part 50. Informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. Examples of this failure include, but are not limited to the following:

In several instances subjects signed incorrect versions of the Informed Consent Documents (ICD) which were not approved by the IRB.

i. Four subjects **(b)(4)** signed the 2002 ICD version in 2004. The 2002 ICD version did not include updated data regarding sample purity rates, subject pregnancy rates, malformation rates, and changes in success rates that would have been available to subjects had the proper version been used.

ii. Two subjects **(b)(4)** and **(b)(4)** signed the 2003 ICD version in 2007. The 2003 ICD version did not include updated data regarding sample purity rates, subject pregnancy rates, malformation rates, miscarriage rates, genetic disease prevalence, and changes in success rates that would have been available to

subjects had the proper version been used.

Your response states that a distribution control procedure will be implemented and that staff will be trained on both the new procedure, and general good clinical practices. If properly implemented and executed, this response appears to be adequate. Please provide copies of the newly created distribution control procedures as well as documentation of the date implemented, dates of training, and a list of staff trained.

2. Failure to ensure an investigation is conducted in accordance with the investigational plan, applicable FDA regulations, and any conditions of approval imposed by FDA and the Institutional Review Board (IRB). [21 CFR 812.100, 21 CFR 812.110(b), and 21 CFR 812.140(a)(1)].

The regulations require clinical investigators to conduct an investigation in accordance with the signed agreement with the sponsor, the investigational plan, all other applicable FDA regulations, and any conditions of approval imposed by the IRB or FDA. 21 CFR 812.100 and 21 CFR 812.110(b). Additionally, an investigator must maintain an accurate, complete, and current record of all correspondence with the sponsor and IRB. 21 CFR 812.140(a)(1). Listed below are several examples where you have failed to meet this requirement. The list below is not intended to be exhaustive.
For example;

- You received approval for continuing review in 2006, and 2008, however, provisional approval for the year 2007 was granted pending submission of updated consent form. To date, there is no record to indicate the required submissions were completed or approved by the IRB.

- The protocol states that procedures for device maintenance are described in the IDE submission. Section I, Part I of the IDE submission requires that "sample **(b)(4)** is replaced with a new one on a **(b)(4)** basis." Section I Part 2 requires "[e]very **(b)(4)** the **(b)(4)** is cleaned and filled with **(b)(4)**" You failed to follow these required procedures for maintenance of the investigational device.

i. The sample **(b)(4)** was not replaced **(b)(4)**. Examples include;

a. The sample **(b)(4)** was not replaced between October 9, 2008 and January 2, 2009.
b. The sample **(b)(4)** not replaced between October 8, 2007 and October 9, 2008.

ii. The device was not **(b)(4)** as required. Examples include;

a. The device was not **(b)(4)** between January 4, 2008 and May 7, 2008.

Your response states that you will ensure all correspondence with the IRB will include clear documentation of the documents that were approved with the version numbers and dates of approval. This response is inadequate in that it does not provide a mechanism of securing future compliance with the IRB's conditions of approval.

Dr. Karabinus responded on your behalf concerning the device maintenance issue. His response states that **(b)(4)** is not performed without changing sample **(b)(4)** and **(b)(4)** is not changed without **(b)(4)** the instrument." This is not consistent with the procedures stated in the sponsor's IDE submission. As a result of nonconformity to the IDE submission, protocol Section XIV, Part B requires the retention of documents showing the dates of, and reasons for, each deviation from the protocol.

3. Failure to submit progress reports on the investigation to the sponsor, the monitor and the reviewing IRB at regular intervals. [21 CFR 812.150(a)(3)].

Clinical investigators are required to prepare and submit progress reports on the investigation to the sponsor, the monitor, and the reviewing IRE at regular intervals, but in no event less often than a yearly. 21 CFR 812.150(a)(3). Additionally, a record of this correspondence is required to be maintained. 21 CFR 812.140(a)(1).

- There was no documentation that annual reports were submitted to the sponsor.

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.

The regulations in 21 CFR Part 812 describe sponsor responsibilities as well as those of investigators. IRB responsibilities are spelled out in 21 CFR Part 56, lnstitutional Review Boards. These three sets of responsibilities overlap to ensure appropriate conduct of clinical studies and the protection of the rights and welfare of participating subjects. Therefore, though the sponsor and IRB involved in your study may have been remiss in fulfilling their responsibilities, you are still held responsible for knowing and following the regulations pertinent to your activities as a clinical investigator in FDA-regulated studies.

In your response to this letter, include documentation that verifies the presence and accuracy of your protocol deviation records, the alterations of your cleaning procedures, and what measures have been taken to ensure staff is aware of, and

adhering to those changes. Please develop procedures and a comprehensive plan to ensure that all required IRB reviews and approvals are completed and documented in a timely manner. Please also develop procedures to ensure that all necessary reports are submitted to the sponsor, IRB and FDA in a timely manner and that records of all correspondence are retained. Please include copies of all training undertaken by you and yom staff to address these concerns as well as projected dates of completion for your updated procedures, dates of training, and list of staff trained.

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. 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/ohrt/irbs/. 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.Traing/CDRHLearn/ucm162015.htm. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. Send your response to: Attention: Linda Godfrey, Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, WO, Bldg. 66, Rm. 3462, 10903 New Hampshire Avenue, Silver Spring, Maryland 20993.

A copy of this letter has been sent to the Los Angeles District Office, 19701 Fairchild, Irvine, CA 92612. Please send a copy of your response to that office.

If you have any questions, please contact Linda Godfrey, (301) 796-5654 Linda.Godfrey@fda.hhs.gov.

Sincerely yours,
/S/
Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and

Radiological Health