

[Home](#) [Inspections, Compliance, Enforcement, and Criminal Investigations](#) [Enforcement Actions](#) [Warning Letters](#)
Inspections, Compliance, Enforcement, and Criminal Investigations



Department of Health and Human Services

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

January 14, 2013

WARNING LETTER

VIA UNITED PARCEL SERVICE

Dear [REDACTED]:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection of your clinical site from September 17 to 28, 2012, by an investigator from the FDA Florida District Office. This inspection was conducted to determine whether activities and procedures related to your participation in the clinical studies of the **(b)(4)**, Premarket Approval (PMA) **(b)(4)** and 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), because it is intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or to affect the structure or function of the body.

We acknowledge receipt of your response to the Form FDA 483, Inspectional Observations, dated November 15, 2012. Because you responded longer than 15 days after the Form FDA 483 was issued, your response was not reviewed or considered with respect to the issuance of this warning letter. See 74 FR 40211. Rather, we will evaluate the response along with any other written material provided as the direct response to this warning letter. This letter requests prompt corrective action to address the violations cited.

The inspection was conducted under a program designed to ensure that data and information contained in requests for IDEs, PMA applications, and Premarket Notification submissions 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 (CFR) Part 812 – IDE and Part 50 - Protection of Human Subjects, which concern requirements prescribed under section 520(g) of the Act, 21 U.S.C. § 360j(g). At the close of the inspection, the FDA investigator presented a Form FDA 483 for your review and discussed the observations listed on the form with you. The deviations noted on the Form FDA 483, and our subsequent review of the inspection report are discussed below:

[REDACTED]

1. Failure to conduct the investigation according to the signed agreement, the investigational plan, applicable FDA regulations, and any conditions of approval imposed by an Institutional Review Board (IRB) or FDA. [21 CFR 812.100 and 812.110(b)]

A clinical 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. The inspection conducted at your site revealed that you failed to follow the investigational plan and did not accurately randomize study subjects.

According to the protocol, subjects were to be assigned to one of three pairs of treatments (test and comparator). Two subjects were given the incorrect randomized mix of comparator and study devices.

a. **(b)(6)** (screening #003) was randomized to receive the treatment pair #3 - **(b)(4)**. However, according to the study administration logs, this subject received the incorrect **(b)(4)**. The drug/device accountability log identifies that the incorrect randomized treatment **(b)(4)** was given instead of the randomized pair #3 **(b)(4)**.

b. **(b)(6)** (screening # 021) was randomized to receive the treatment pair #3 - **(b)(4)**. However, this subject received a mix of treatment pair #3 - **(b)(4)** and treatment pair #1 or 2 - **(b)(4)**.

Your failure to accurately randomize subjects according to the investigational plan has compromised the reliability of the study data. Furthermore, subsequent treatment of randomized study subjects with the incorrect device treatment pair has introduced bias into the study. Your actions can compromise FDA's review and statistical analysis of the data submitted from your site.

In your response to this letter, you should provide documentation of all corrective actions taken or planned to assure that you will abide by the IRB approved protocol and investigator agreement for this and future studies.

2. Failure to ensure that an investigation is conducted in accordance with the signed agreement, investigational plan, and applicable FDA regulations for the control of devices under investigation; and failure to maintain accurate, complete, and current records of disposition of a device. [21 CFR 812.100 and 21 CFR 812.140(a)(2)(ii-iii)]

A clinical investigator is responsible for conducting an investigation in accordance with the signed agreement, investigational plan, and applicable FDA regulations for the control of devices under investigation, and for maintaining accurate, complete, and current records of receipt, use, or disposition of a device.

The FDA inspector found no documentation to confirm when or how disposal of used or unused devices was accomplished. There was no device accountability record documenting the disposition of all devices, such as whether devices were used in a subject, used in other subjects, unused, or returned to the sponsor.

Your failure to maintain device accountability records is a serious violation of your responsibility as a clinical investigator. This can potentially lead to misuse of the investigational device by untrained persons on subjects for which the device is not indicated. These patients could be placed at increased risk of medical complications including cosmetic disfigurement.

In your response to this letter, please provide documentation of the underlying cause of your device accountability problems and describe the processes you have undertaken to correct and prevent recurrence of the problems. Please also provide documentation of the actions you have taken or plan to take to maintain accurate, complete, and current records of receipt, use, or disposition of your investigational devices.

3. Failure to properly document informed consent, to maintain accurate, complete and current records evidencing informed consent, and to conduct an investigation according to applicable FDA regulations for protecting the rights, safety, and welfare of subjects under the investigator's care. [21 CFR 50.27(a) 21 CFR 812.140(a)(3)(i), and 21 CFR 812.100]

A clinical investigator is responsible for ensuring that informed consent is obtained in accordance with applicable FDA regulations.

a. Although the IRB approved the consent form on October 15, 2010, and October 18, 2010, 25 of 33 subjects were initially consented with an unapproved version of the informed consent template upon enrollment and injection with the study product.

Examples of these failures include, but are not limited to the following:

Subject #	Initial unapproved consent signed	Enrollment and injection	IRB consent signed
(b)(6)	2-11-2011	2-11-2011	5-25-2011
(b)(6)	2-09-2011	2-9-2011	5-18-2011
(b)(6)	2-11-2011	2-11-2011	8-22-2011
(b)(6)	2-23-2011	2-23-2011	4-6-2011

Failure to utilize the IRB-approved informed consent document violates the rights, safety, and welfare of subjects enrolled in the study. The unapproved consent document failed to provide the complete information that is supplied in the IRB-approved version, including whom to contact for answers to pertinent questions and whom to contact in the event of research related injury. This information is important to ensure subject safety in case they experience medical complications and need prompt medical assessment or treatment.

b. You failed to maintain original consent documents. The initial unapproved version of the signed informed consents, reportedly obtained at enrollment of seven subjects **(b)(6)** were not available during the FDA inspection.

c. You failed to provide copies of the signed informed consent forms to the subjects.

This failure brings into question whether these subjects were afforded the opportunity to provide adequate, knowledgeable, informed consent sufficient to proceed with the study and to understand the risks and benefits of participating.

In your response to this letter, please provide documentation of the corrective actions taken or planned to assure that consent from all study subjects is obtained and records are maintained. Please provide a plan to assure that subjects are presented with and sign the most recent IRB-approved consent document. Within your plan, please address:

- how and when additional informed consents will be required of subjects when the protocol changes dictate,
- how you will assure that subjects will be provided with a copy of their consent,
- standard operating procedures directed at obtaining proper informed consent, and
- how you will educate and document that all staff have received training in the process of human subject protection.

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

A clinical investigator is responsible for maintaining accurate, complete, and current records of each subject's case history and exposure to the device, which includes the case report forms (CRFs) and supporting data. You failed to adhere to the above-stated regulation in that several CRFs were not complete. Examples of your failure include, but are not limited to, the following:

- Screening and subject number identification were left blank on the CRFs for most subjects in the study.
- The investigator and observer names and signatures noting when an intervention was performed were not completed on most CRFs.

Accurate identification of CRFs is essential to avoid transcription errors and mixing subject records. This leads to inaccuracies and makes the data unverifiable and unreliable. Inclusion of all required elements in the CRFs is essential for compilation of the data necessary for study evaluation.

In your response to this letter, please provide documentation of the corrective actions taken or planned to assure that all study related records including case report forms are accurate, complete, current, and, where required, signed.

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 15 working days of receiving this letter, please provide documentation of the actions that you have taken or will take to correct these violations and to prevent the recurrence of similar violations in current or future studies for which you are the clinical investigator.

Your response should reference "CTS # P120013/E004" and be sent to:

Attention: Isatu Bah, MS, RN
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance
Division of Bioresearch Monitoring
10903 New Hampshire Avenue
Building 66, Room 3461
Silver Spring, Maryland 20993-0002.

A copy of this letter has been sent to FDA's Florida District Office, 555 Winderley Place, Suite 200, Maitland, FL 32751. Please send a copy of your response to that office.

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.

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>¹.

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 and a plan for monitoring the effectiveness of your corrective actions.

If you have any questions, please contact Isatu Bah at 301-796-5655 or by email at Isatu.Bah@fda.hhs.gov.

Sincerely yours,
/S/
Steven D. Silverman
Director
Office of Compliance
Center for Devices and
Radiological Health

Page Last Updated: 02/21/2013

Note: If you need help accessing information in different file formats, see [Instructions for Downloading Viewers and Players](#).