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## Inspections, Compliance, Enforcement, and Criminal Investigations

[REDACTED] 2/21/14



Department of Health and Human Services

Public Health Service  
Food and Drug Administration  
Silver Spring, MD 20993

### WARNING LETTER

FEB 21, 2014

**CERTIFIED MAIL**  
**RETURN RECEIPT REQUESTED**



14-HFD-45-02-02

Dear Dr. [REDACTED]:

This Warning Letter informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted at your clinical site between June 5 and 25, 2013. Mr. Thomas Hansen, representing the FDA, reviewed your conduct of the following clinical investigations:

- Protocol **(b)(4)**, "**(b)(4)**," of the investigation drug **(b)(4)**, performed for Dr. **(b)(4)**
- Protocol **(b)(4)**, "**(b)(4)**," of the investigational drug **(b)(4)**, performed for **(b)(4)**

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of FDA-regulated research to ensure that the data are scientifically valid and accurate, and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

At the conclusion of the inspection, Mr. Hansen presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your July 11, 2013 written response to the Form FDA 483.

From our review of the FDA Establishment Inspection Report, the documents submitted with that report, and your July 11, 2013 written response, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We wish to emphasize the following:

**1. You failed to personally conduct or supervise the clinical investigations [21 CFR 312.60].**

When you signed the Statement of Investigator (Form FDA 1572) for the above-referenced clinical trials, you agreed to take on the responsibilities of a clinical investigator at your site. Your general responsibilities

as a clinical investigator include ensuring that the clinical trials are conducted according to the signed investigator statement, the investigational plan, and applicable regulations; protecting the rights, safety, and welfare of subjects under your care; and ensuring control of drugs under investigation [21 CFR 312.60]. By signing Form FDA 1572, you specifically agreed to personally conduct the clinical trial or to supervise those aspects of the trial that you did not personally conduct. While you may delegate certain study tasks to individuals qualified to perform them, as a clinical investigator you may not delegate your general responsibilities. Our investigation indicates that your supervision of personnel to whom you delegated study tasks was not adequate to ensure that the clinical trial was conducted according to the signed investigator statement, the investigational plan, and applicable regulations, and in a manner that protects the rights, safety, and welfare of human subjects.

Specifically, for Protocol **(b)(4)**, you failed to supervise adequately the individuals to whom you delegated study tasks. Your failure to supervise adequately the conduct of Protocol **(b)(4)** led to many of the violations noted in this letter. These violations include, but are not limited to, enrollment of subjects into the protocol when approval by the Columbia University Medical Center (CUMC) Institutional Review Board (IRB) had lapsed; failure to obtain informed consent from 28 of 50 enrolled subjects; and randomization and administration of investigational drug to 10 subjects before obtaining their informed consent to participate in the study.

In your July 11, 2013 written response, you acknowledged that you "did not provide adequate supervision or delegate the responsibilities of conducting the study appropriately." You also acknowledged that it was your responsibility to ensure that the IRB-approved protocol was followed, and you stated that you "delegated this responsibility without providing the proper oversight."

As the clinical investigator, it was your ultimate responsibility to ensure that the studies were conducted properly and in compliance with FDA regulations in order to protect the rights, safety, and welfare of study subjects and to ensure the integrity of the study data. Your lack of supervision and oversight over Protocol **(b)(4)** raises significant concerns about the adequacy of your protection of study subjects enrolled at you site in the studies mentioned above and also raises data integrity concerns generated for Protocol **(b)(4)**.

## **2. You failed to obtain informed consent in accordance with the provisions of 21 CFR part 50 [21 CFR 312.60 and 21 CFR 50.20].**

As a clinical investigator, it is your responsibility to obtain informed consent in accordance with 21 CFR part 50. FDA's regulations at 21 CFR 50.20 state that, except as provided in 21 CFR 50.23 and 21 CFR 50.24, no investigator may involve a human being as a subject in research covered by the regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. You failed to obtain legally effective informed consent. Specifically:

a. You failed to obtain informed consent from the following 28 of 50 subjects who were enrolled in Protocol **(b)(4)**: Subjects C1, C4 through C7, C9 through C12, C17, C19, C20, C22, C26, C28, C30, C31, C33, C34, C37 through C42, C45, A3, and A5.

b. You enrolled 10 subjects into Protocol **(b)(4)** and gave them investigational drug before each signed the informed consent document. These subjects are listed in the Table below.

<b>Subject</b>	<b>Date Subject first given investigational drug</b>	<b>Date Subject first signed the Informed Consent Document</b>
C15	September 15, 2010	December 10, 2010
C16	September 15, 2010	September 22, 2010
C21	November 28, 2010	December 17, 2010
C24	December 17, 2010	December 23, 2010
C25	December 20, 2010	December 28, 2010
C32	May 19, 2011	June 16, 2011
C36	January 26, 2011	February 9, 2011
C43	April 7, 2011	April 26, 2011
C44	May 10, 2011	May 27, 2011
C47	April 29, 2011	May 26, 2011

In your July 11, 2013 written response to the Form FDA 483 [pages 3-4] you agreed that you failed to obtain consent from the 28 subjects listed in Item 2.a. above and that you gave investigational drug to the additional 10 enrolled subjects listed in item 2.b. above, prior to subjects signing the informed consent document. In addition, in that written response you stated, "I acknowledge and take full responsibility for not providing the instruction and oversight of the research staff delegated to recruiting and obtaining informed consent."

We acknowledge you summarized, in the written response, actions that the Columbia University Medical Center Institutional Review Board (CUMC IRB) and the Department of Obstetrics and Gynecology (Department) have taken. You indicated that after serious noncompliance and the potential risk to subjects was discovered, on August 19, 2011, the CUMC IRB and the Department suspended Protocol **(b)(4)**, the Department performed an audit of all available study records and, at the direction of the IRB, all 50 subject were notified of the violations in the consent process and study procedures.

We also acknowledge your corrective action plan that includes the following:

- Re-education of investigators involved in Protocol **(b)(4)**;
- Mandatory Department approval of all research so that appropriate safeguards and monitoring can be initiated;
- Establishment of a Department requirement for assigning a research coordinator to each investigator-initiated FDA regulated research study;
- Performance of quarterly monitoring by the Department Quality Assurance (QA) Research Monitor, and;
- Use of an Informed Consent Process Checklist to assist in the documentation of the consent process.

Your written response is inadequate as it relates to the findings noted in Item 2 above. We are concerned that the majority of the corrective actions appear to represent actions taken by Columbia University Medical Center and do not reflect corrective actions that you personally have taken. Please note that, as the clinical investigator, you are ultimately responsible for ensuring that informed consent is obtained in accordance with 21 CFR part 50.

We are also concerned about your plans to use the Informed Consent Process Checklist to ensure that the consent process is documented appropriately. This checklist does not address the timing of consent and, therefore, does not appear adequate to acquire informed consent prior to a subject's participation in clinical research. In addition, the checklist refers to consent forms printed from "Rascal." We request clarification on the "Rascal" system as it relates to study data tracking, such as informed consent.

Your failure to obtain informed consent prior to involving subjects in research jeopardizes the safety and welfare of subjects by denying them an opportunity to assess the risks and benefits of their participation in the clinical investigation.

### **3. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].**

As a clinical investigator, you are required to ensure that your clinical studies are conducted in accordance with the investigational plan. The investigational plan for Protocol **(b)(4)** required you to administer the protocol-specified dose of investigational drug to each subject according to their assigned study arm, and to obtain study-related laboratory tests. You failed to adhere to these requirements. Examples of this failure include but are not limited to the following:

Protocol **(b)(4)** contained two study arms: (1) a "traditional" **(b)(4)** treatment arm, and (2) a "stair-step" arm. The "traditional" treatment arm required that the subject receive 50 mg of **(b)(4)** daily for 5 days on Day 5 - 9 of the first menstrual cycle during the study. If the subject did not develop a positive response (i.e., follicles of at least 17 mm in size) after the first menstrual cycle, the protocol required that the dose be increased to 100 mg on the second menstrual cycle. If the subject did not develop a positive response after the second cycle, the protocol required that the dose be increased to 150 mg on the third cycle. The "stair-step" arm required that the subject receive the same dosing of **(b)(4)** (50 mg to 150 mg) in an

attempt to induce a positive response, but in a shorter timeframe and without having to wait for the next menstrual cycle before increasing the **(b)(4)** dose from 50 mg to 100 mg or from 100 mg to 150 mg.

For Protocol **(b)(4)**, four subjects were not dosed according to their protocol-specified study arm (standard dosing or stair-step dosing). Specifically:

a. Subject C4 was enrolled in Protocol **(b)(4)** on October 10, 2010, and assigned to the "traditional" or "standard" dosing arm. The subject's dosing log shows that Subject C4 received the protocol-required **(b)(4)** dose of 50 mg and 100 mg during Cycles 1 and 2, respectively. However, the dosing log shows that for Cycle 3, the subject again received 100 mg daily for 5 days rather than 150 mg daily for 5 days as required by the protocol. The Progress Note Addendum for Subject C4 states that the subject responded to 50 mg of **(b)(4)** and no further assessment was needed, but this statement is not supported by the dosing log.

In your written response to the Form FDA 483, you indicate that Subject C4 received 50 mg daily for 5 days, responded with the development of one preovulatory follicle, and then exited the study. Your response is inadequate because it lacks supporting documentation and an explanation as to why the dosing records described above conflict with the Progress Note Addendum and your response.

b. Subject C6 was enrolled in Protocol **(b)(4)** on December 17, 2010, and assigned to the "stair-step" dosing arm. The subject's dosing log shows that Subject C6 received **(b)(4)** 50 mg daily from January 11 to 15, 2011, and from March 31 to April 6, 2011, and then received 75 mg daily from April 7 to 14, 2011, rather than the protocol-required stair-step dosing. The Progress Note Addendum for Subject C6 states that the subject responded to 50 mg of **(b)(4)** and became pregnant. The Progress Note Addendum conflicts with the dosing log.

In your written response to the Form FDA 483, you indicate that Subject C6 received 50 mg of **(b)(4)** for 5 days, responded with the development of a preovulatory follicle, and exited the study. Your response is inadequate because it lacks supporting documentation and an explanation as to why the subject's dosing log conflicts with your response.

c. Subject C19 was enrolled in Protocol **(b)(4)** on December 13, 2010 and assigned to the "stair-step" dosing arm. The subject's dosing log shows that Subject C19 received **(b)(4)** 25 mg daily from December 13 to 17, 2010, and from February 15 to 19, 2011, rather than the protocol-required stair-step dosing. The Progress Note Addendum notes the subject received 50 mg of **(b)(4)** for each cycle. The Progress Note Addendum conflicts with the dosing log.

In your written response to the Form FDA 483, you state that Subject C19 "had a hyper-response to 50 mg for 5 days and exited the study; she required a dose decrease with her next cycle." Your response is inadequate because it lacks supporting documentation and an explanation as to why the subject's dosing log and Progress Note Addendum conflict with your response.

d. Subject C35 was enrolled in Protocol **(b)(4)** on January 21, 2011 and assigned to the "traditional" or "standard" dosing arm. According to the subject's dosing log, Subject C35 received **(b)(4)** 100 mg daily for 5 days during Cycles 1, 2, and 3 rather starting with the protocol-required dose of 50 mg in Cycle 1 and progressing to 100 mg and 150 mg in Cycles 2 and 3, respectively. The Progress Note Addendum indicates the subject's first treatment cycle was for 50 mg, followed monthly by three 100 mg cycles.

In your written response to the Form FDA 483, you indicate that Subject C35 received **(b)(4)** 50 mg for 5 days, had a delayed response, had a dose increase to **(b)(4)** 100 mg at the next cycle, and then achieved a normal response and exited the study. Your response is inadequate because it lacks supporting documentation and an explanation as to why the subject's dosing log conflicts with your response as well as the Progress Note Addendum.

In your July 11, 2013 written response to the Form FDA 483, you stated, "I agree that the IRB-approved protocol-specific dosing regimens were not followed for all subjects, resulting in protocol violations." You further explained that, "A review of subjects' charts noted that many of the subjects were treated according to clinical standards, instead of adhering to the strict dose and schedule in the IRB-approved protocol."

In your written response, you also acknowledged your responsibility to ensure that the IRB-approved study protocol is followed and acknowledged that you were "responsible for these errors." You also stated that you "will supervise and monitor for protocol violations and report to the IRB and the sponsor, accordingly."

Your written response is inadequate because you failed to provide sufficient details with respect to your corrective action plan. For example, you did not provide details regarding how you will carry out your plan to supervise and monitor protocol violations. Without having these details, we are unable to determine whether your corrective action appears sufficient to prevent similar violations in the future.

Failure to administer investigational drug to subjects according to the protocol-required dosing schedule compromises the validity and integrity of data generated at your site for Protocol **(b)(4)**.

**4. You failed to assure that an IRB that complies with the requirements set forth in part 56 was responsible for the initial and continuing review and approval of the proposed clinical study [21 CFR 312.66].**

As a clinical investigator, you are required to assure that an IRB that complies with 21 CFR part 56 reviews and approves a proposed clinical investigation. You failed to assure that an IRB that complies with 21 CFR part 56 reviewed and approved a proposed clinical study.

Specifically, IRB approval to conduct Protocol **(b)(4)** lapsed from March 30 to June 3, 2011. During this lapsed period, you enrolled six subjects (Subjects C42 through C47) into this protocol and gave them the investigational drug.

In your July 11, 2013 written response to the Form FDA 483, you acknowledged that you "failed to ensure that continuing IRB approval was maintained" and that "subjects were enrolled and treated during a lapse in IRB approval." In that response, you also described corrective actions that you will take, including monitoring the protocol for continuing IRB approval and ensuring that no study-related procedures are performed without IRB approval or during a period in which IRB approval has lapsed.

Your response is inadequate with respect to the conduct of study activities without IRB approval. Specifically, you did not provide details regarding how you will ensure that you will monitor protocols for continuing IRB approval or how you will ensure that no study-related procedures are performed without IRB approval or during a period in which IRB approval has lapsed. Without having these details, we are unable to determine whether your corrective action appears sufficient to prevent similar violations in the future.

Your failure to ensure continuing IRB review and approval of Protocol **(b)(4)** impeded the IRB's ability to review your application to conduct Protocol **(b)(4)** and make a determination regarding the adequacy of that application.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational drug. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You should address these deficiencies and establish procedures to ensure that any ongoing or future studies will comply with FDA regulations.

Within fifteen (15) working days of your receipt of this letter, you should notify this office in writing of the actions you have taken to prevent similar violations in the future. Failure to address the violations noted above adequately and promptly may result in regulatory action without further notice. If you believe you have complied with FDA regulations, include your reasoning and any supporting information for our consideration.

If you have any questions, please contact Constance Cullity, M.D., M.P.H., at 301-796-3397; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Constance Cullity, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Enforcement Branch  
Division of Good Clinical Practice Compliance