Elizabeth E. Houser, MD 5/25/12

Dear Dr. Houser:

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 December 6, 2010, and January 6, 2011, by Mr. Robert Lorenz, representing the FDA, to review your conduct of the following clinical investigations of the investigational drug (b)(4), performed for (b)(4):

- Protocol # (b)(4), "(b)(4)"; and
- Protocol # (b)(4), "(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 involved in those studies have been protected.

At the conclusion of the inspection, Mr. Lorenz presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your January 14, 2011, written response to the Form FDA 483.

From our review of the establishment inspection report and the documents submitted with that report, and your January 14, 2011, written response, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We wish to emphasize the following:
1. You repeatedly or deliberately submitted to FDA or to the sponsor false information in any required report [21 CFR 312.70(a)].

As a clinical investigator for Protocol (b)(4), you were required to conduct the following assessments and report these to the sponsor: (1) Clinical Global Impression (CGI) of Severity, and (2) CGI of Efficacy Index. FDA has concluded that as the clinical investigator for Protocol (b)(4), you submitted false information to the sponsor through the submission of these required assessments. Specifically:

For Subject 27881 enrolled into Protocol (b)(4), the records for the following assessments indicate that they were completed by Dr. (b)(6), your sub-investigator: (1) CGI of Severity for Visits 2, 4, 5, 6, and 7; and (2) CGI of Efficacy Index for Visits 4, 5, 6, and 7. However, according to Dr. (b)(6), she did not conduct these assessments. The study coordinator, (b)(6), falsified these records by entering Dr. (b)(6)'s name as having completed the assessments.

Although this violation was not listed on the Form FDA 483, our field investigator discussed this violation with you and Dr. (b)(6) during the inspection. At that time, you indicated that the site management organization (SMO) with which you contracted to assist in the conduct of Protocol (b)(4) had provided you with study coordinator (b)(6), and that you had used this SMO for numerous prior studies. During the inspection, you did not indicate whether you investigated to determine if any other studies you conducted contained entries from (b)(6), purporting to be assessments conducted by study staff who did not actually conduct the assessments.

As the clinical investigator, it is your responsibility to ensure that the data collected from study subjects are accurate and can be relied upon in any analyses of the study endpoints. When you signed the Statement of the Investigator, Form FDA 1572, you agreed to maintain adequate and accurate records and to ensure that you will comply with FDA regulations related to the conduct of the clinical investigations of the investigational drugs; and you agreed to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting their commitments. Furthermore, your signature constitutes both your affirmation that you are qualified to conduct the clinical investigation and your written commitment to abide by FDA regulations in the conduct of the clinical investigations. The use of falsified information significantly compromises the study integrity, as well as the reliability and validity of the data.

2. You failed to ensure that the investigation was conducted according to the investigational plan [2: 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) requires that certain evaluations be performed at clinic visits, and that the CGIs of Severity and Efficacy be performed by a clinical expert. In addition, Protocols (b)(4) and (b)(4) both prohibit the use of certain medications by subjects and have defined inclusion criteria for each subject. You failed to adhere to these requirements. Specifically:

a. Protocol (b)(4) required that the following evaluations be performed at the clinic during Visits 2 (Baseline) 4, 5, 6, and 7: Blood pressure and pulse rate, weight, Beck Scale for Suicidal Ideation (BSS), Female Sexual Distress Scale – Revised (FSDS-R), Female Sexual Function Index (FSFI), and assessments for any adverse events and concomitant therapy. The protocol further required that assessment of inclusion/exclusion criteria was to be performed at the clinic at Visit 2 (Baseline); CGI of Efficacy Index and assessment of medication compliance were to be performed at the clinic during Visits 4, 5, 6, and 7; and an electrocardiogram (ECG) an laboratory tests were to be taken at the clinic during Visit 7. In addition, the protocol required that the CGI assessments be performed by an expert clinician who holds one of the following credentials: D.O., M.D., Clinical Ph.D. psychologist, sex therapist, Physician’s Assistant or Nurse Practitioner.

For Subject 27881, Visits 2, 4, 5, 6, and 7 were conducted off-site instead of at the clinic, as required by the protocol. In addition, the CGIs of Severity and Efficacy for these visits were conducted by your study coordinator who does not hold any of the required credentials and was therefore not qualified to conduct these assessments.

b. Protocol (b)(4), Section 6.2.1 requires laboratory tests, including prolactin levels, at Week-1 (Visit 1). This section of the protocol further requires that all clinically significant (in the investigator’s judgment) abnormal laboratory tests be repeated before any subject can be enrolled.

Subject 27839 was enrolled into the study and was provided with study drug at Visit 2 on July 20, 2007, before the prolactin laboratory results were available. The subject’s prolactin result was provided in a laboratory report dated July 26, 2007, and was at a level (61 ng/mL) that you deemed clinically significant. As a result, Subject 27839 did not meet inclusion criteria and should not have been enrolled.
c. Protocol (b)(4), Section 10.3.1 (List of Prohibited Medications) and Protocol (b)(4), Section 10.1.1 (List of Prohibited Medications) prohibit the use of hormonal agonists. Subject 27884 was on a continuing dose of 100 mg/day Prometrium (a hormonal agonist) beginning September 22, 2005. Therefore, Subject 27884 was inappropriately enrolled into both studies.

In your January 14, 2011, written response to the Form FDA 483, you state that you have done the following: You terminated the services of your site management organization; promptly reported the off-site visits to the sponsor; conducted an audit of study files; created a new subject enrollment Standard Operating Procedure (SOP); and developed additional plans that were not included in your response, to be implemented in your research department. In addition, you agreed that Subjects 27839 and 27884 should not have been enrolled.

We find your response inadequate, because you failed to provide documentation of the corrective actions implemented at your clinical site. Without adequate documentation, we cannot assess whether or not the corrective actions are appropriate. You did not include in your response the criteria used in your internal audit, copies of your new SOP for subject enrollment, or training your study staff received on the new SOP. Further, you did not specifically identify what the additional plans developed by your research department were intended to address.

In your response to this letter, please provide documentation of your corrective actions. This response should include a copy of the audit plan you used to verify that study coordinator (b)(6) did not: (1) conduct any other assessments that she was not qualified to do; (2) attribute any such assessments to qualified persons who did not actually conduct the assessments; or (3) conduct additional unapproved off-site visits.

We acknowledge your statement in your response that you have closed your research department and that you "had several plans and actions to be taken in our Research Department that are not included in this letter. Due to department closure[,] several of these items were not completed and/or implemented." However, please note that it remains your responsibility to address the issues noted in this letter.

Enrollment of subjects who do not meet eligibility criteria, the conduct of CGIs by unqualified staff, and false attribution of CGIs of Severity and Efficacy to a sub-investigator jeopardize subject safety and welfare and raise concerns about the validity and integrity of the data collected at your site.

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 be in compliance with FDA regulations.

Within fifteen (15) working days of your receipt of this letter, you should notify this office in writing of the action 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.

We acknowledge your assurance that you do not intend to perform clinical investigations (clinical trials) in the future. If you should change your mind about conducting clinical trials, please inform this office of your plans.

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
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5354
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely yours,
/S/
Leslie K. Ball, M.D. Acting Director