Dear Dr. Lobo:

This Warning Letter informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted at your research office at Columbia University Medical Center (CUMC) between June 5 and June 25, 2013. Mr. Thomas Hansen, representing FDA, reviewed your conduct as the sponsor of a clinical investigation (Protocol (b)(4)) of the investigational drug (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:

**Failure to ensure proper monitoring of the investigation and failure to ensure that the investigation is conducted in accordance with the general investigational plan and protocols contained in the IND [21 CFR 312.50 and 312.56(a)].**
FDA regulations require that sponsors ensure proper monitoring of clinical investigations and ensure that their clinical investigators conduct the investigations in accordance with the protocols contained in the Investigational New Drug file (IND). Our investigation found that you failed to ensure proper monitoring of Protocol (b)(4), and that you did not ensure that a clinical investigator conducted the investigation in accordance with a protocol contained in the IND. As a result of inadequate monitoring, you did not identify and correct in a timely manner a clinical investigator’s failure to obtain informed consent from subjects, in accordance with FDA regulations; a clinical investigator’s failure to ensure ongoing Institutional Review Board (IRB) approval of the protocol; and a clinical investigator’s failure to administer the dose of investigational drug to subjects, according to their protocol-specified treatment arm.

1. As the sponsor for Protocol (b)(4), your monitoring failed to identify and correct a clinical investigator’s failure to obtain informed consent from subjects, in accordance with the provisions of 21 CFR 321.60 and 50.20. Specifically:

   a. Your monitoring did not identify and correct the clinical investigator’s failure to obtain informed consent from the following 26 of 50 subjects who were enrolled into Protocol (b)(4):
      Subjects C1, C4 through C7, C9 through C12, C17, C19, C20, C22, C26, C28, C30, C31, C33, C34, C37 through C41, C45, and A5.

   b. Your monitoring did not identify and correct the clinical investigator’s failure to obtain informed consent before administering investigational drug to the following 12 subjects who were enrolled into Protocol (b)(4):

2. Your monitoring did not identify and correct a clinical investigator’s failure to ensure that an IRB reviews and approves a proposed clinical investigation, in accordance with 21 CFR part 56. Specifically, IRB approval to conduct Protocol (b)(4) lapsed from March 31 to June 3, 2011. During this lapsed period, the clinical investigator enrolled 6 subjects (Subjects C42 through C47) and treated them with investigational drug.

3. Your monitoring failed to ensure that the investigation was conducted in accordance with the investigational plan.

Protocol (b)(4) contained two study treatment arms: (1) a “traditional” or “standard” (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) (i.e., 50 mg, 100 mg, and 150 mg) in an attempt to induce a positive response, but within a shorter time frame and without waiting for the next menstrual cycle before increasing the (b)(4) dose from 50 mg to 100 mg or from 100 mg to 150 mg.

Your monitoring did not identify and correct a clinical investigator’s failure to administer the correct dose of study drug to 4 subjects. Specifically:

   a. Subject C4 was enrolled in Protocol (b)(4) on October 10, 2010, and was assigned to the “traditional” or “standard” dosing arm. The subject’s dosing log shows that Subject C4 received the protocol-required (b)(4) doses 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; however, this statement is not supported by the dosing log.
b. Subject C6 was enrolled in Protocol (b)(4) on December 17, 2010, and was 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 the same dose again from March 31 to April 6, 2011; the subject then received 75 mg 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. Thus, the Progress Note Addendum conflicts with the dosing log.

c. Subject C19 was enrolled in Protocol (b)(4) on December 13, 2010, and was 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 the same dose again from February 15 to 19, 2011, rather than the protocol-required stair-step dosing. The Progress Note Addendum notes that the subject had, in the past, had a strong response to a dose of 50 mg of (b)(4).

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

We recognize that the Form FDA 483 issued to you does not include the findings noted in Items 1 through 3 above, and that your written response therefore did not address these specific issues. However, in the July 11, 2013, written response to the Form FDA 483, you acknowledged that you were responsible for monitoring the progress of Protocol (b)(4), and that you failed to discover that the clinical investigator was not complying with the IRB-approved protocol, the consent process, and the documentation of study procedures. You also acknowledged that upon finding noncompliance, you were responsible for either promptly securing compliance or ending the investigator's participation in the study.

We acknowledge that in the July 11, 2013, written response signed by you and the Chair of the Department of Obstetrics and Gynecology at the University of Columbia Medical Center, you provided a corrective action plan that includes the following:

- Use of the Columbia University Clinical Trials Office (CTO) Data-Monitoring Plan templates and forms
- Completion of online training about FDA sponsor-investigator responsibilities, given by the Columbia University Clinical Trials Office; one-on-one training from the Columbia University IND/IDE Assistance Program (IAP); and recertification by the CITI online human subjects research training, and by your Institutional Review Board (IRB) for FDA-regulated research
- Commitment to ensure that all future studies will be monitored through the Departmental Quality Assurance Program, and that all staff and research coordinators involved in the management of your studies will be properly trained
- Partnering with the Clinical Trials Office's IAP to provide training, education, and guidance about the responsibilities of holding an IND
- Utilizing the monitoring-plan guidelines and monitoring tools of the Clinical Trials Monitoring Assistance Program (CTMAP), implemented in October of 2011
- Ensuring that investigators and research personnel have adequate experience and training, shown by demonstrating their understanding of the IRB-approved protocol, the investigational plan, regulatory requirements, and Good Clinical Practice (GCP). In order to demonstrate an understanding of these requirements, investigators and research personnel will have to successfully complete institutional training requirements, such as the Collaborative Institutional Training Initiative (CITI) FDA-regulated research training; the CITI Human Subjects Protection course; and the Columbia University Clinical Research Coordinator training program, which was implemented in October 2010. Fulfillment of these training requirements will be documented in a Training Log.
Ensuring drug accountability by requiring that all investigational drugs be dispensed from the Research Pharmacy, and by requiring that investigational drug supply will be prescribed only by trained qualified investigators and subinvestigators designated on the FDA 1572.

Following the Columbia IRB policy requiring (1) that a Form FDA 1572 be submitted with all protocols; (2) that all initial IND/IDE applications be reviewed and approved by the IAP before they are submitted to FDA; (3) that a final copy of all FDA submissions be submitted to the IAP; and (4) that a Regulatory Binder Checklist be maintained to assist in maintaining these records.

Requiring investigators to record adverse events in an Adverse Events Log to ensure adequate and timely review and recording of adverse events.

In addition to your personal commitments to reform research practices, the July 11, 2013, response states that the University of Columbia Medical Center has implemented the following:

- CUMC Department Chair and Senior Director of Research Administration approval of all research protocols before IRB approval.
- Implementation of a more formalized Quality Assurance (QA) Monitoring Program, including appointment of a QA Research Monitor to conduct continuing review and monitoring for all investigator-initiated trials.
- Monthly Departmental educational meetings.
- Requiring an orientation program for new personnel involved in clinical research.
- Working with the Columbia University CTO and the IRB to ensure compliance with institutional requirements.

For the most part, the corrective actions noted above appear to be adequate. However, we are concerned about your plans to use Columbia University’s Data-Monitoring Plan Template, Guidance, and Instructions to Investigators to ensure adequate monitoring of future studies for which you are the sponsor. Specifically, we note that while this document provides a general template for drafting a data-monitoring plan, it does not itself provide any guidance on the timing and frequency of monitoring the specific monitoring activities to be performed; and how the sponsor’s monitor will interact with the clinical investigator to correct observed violations and bring the investigator into compliance. In light of this deficiency, we are unable to determine how you will ensure that monitoring is properly carried out in any studies that you may sponsor. Without having these details, we are unable to determine whether this corrective action is sufficient to prevent similar violations in the future.

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 actions you have taken to prevent similar violations in the future. Failure to explain the violations noted above adequately and promptly may result in regulatory action without further notice. If you believe that 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.
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Division of Good Clinical Practice Compliance  
Office of Scientific Investigations  
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Sincerely yours,  
{See appended electronic signature page}  
Sean Y. Kassim, Ph.D.  
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Office of Scientific Investigations  
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/s/  
SEAN Y KASSIM  
04/18/2014

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