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Inspections, Compliance, Enforcement, and Criminal Investigations

[REDACTED] . 8/26/11



Department of Health and Human Services

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

WARNING LETTER

**CERTIFIED MAIL
RETURN RECEIPT REQUESTED**

Ref: 11-HFD-45-08-0

[REDACTED]

Dear Dr. [REDACTED]

Between August 2 and August 20, 2010, Heika R. Tait, representing the U.S. Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (Protocol **(b)(4)**, titled "**(b)(4)**") of the investigational drugs **(b)(4)** and **(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 research and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report, the documents submitted with that report, and your September 10, 2010, written response to the Form FDA 483 ("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 are aware that at the conclusion of the inspection, Heika R. Tait presented and discussed with you Form FDA 483, Inspectional Observations.

We wish to emphasize the following:

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

Your general responsibilities as a clinical investigator include ensuring that the clinical trial is 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]. Examples of your failure to follow the investigational plan include, but are not limited to, the following:

a. Section 3 of the protocol specified that subjects be randomized to receive either (b)(4) or (b)(4). However, according to your November 2, 2009, report to the Institutional Review Board (IRB), Subject 6002 received a combination of the investigational drugs (b)(4) and (b)(4) on July 29, 2009, even though this subject, one of only two enrolled at your site, was randomized to receive only (b)(4). In addition, according to an October 20, 2009, letter from the sponsor addressed to you, analyses of post-infusion blood samples for Subject 6002 indicated the presence of both (b)(4) and (b)(4).

b. Section 9.2 of the protocol specified that records of adverse events must have certain adverse event attributes assigned by the investigator, including, but not limited to, the following: event description (with detail appropriate to the event); and assessment of relatedness to investigational product (IP), chemotherapy, or the combination of IP and chemotherapy.

These attributes were not recorded in the adverse events log for Subject 6002.

Failure to randomize subjects properly and to capture adverse event attributes raises concerns about the extent to which subjects' rights, safety, and welfare were protected, and also raises concerns about the reliability of the data at your site. Your written response states generally that you will conduct research studies "under the umbrella of US Oncology Research going forward as there are checks and balances in place" to prevent a recurrence of the violations cited in this letter, and includes new Standard Operating Procedures (SOPs) for drug accountability. However, as the clinical investigator, it was your responsibility to ensure that the study was conducted in accordance with the investigational plan; and US Oncology Research's policies, procedures, and activities do not negate your responsibility as the clinical investigator.

2. You failed to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects [21 CFR 312.62(a)].

a. The Return of Investigation Product for Destruction Form indicates that 4 vials of investigational product ((b)(4)) were missing. You have no records to account for the disposition of these vials.

b. During the inspection, you and your staff informed Investigator Tait that the investigational drugs were stored at one office, and were transported to another office, where the subjects received the drugs. However, there are no records to document this transfer of the investigational drugs.

c. The protocol required that an IP Accountability and Preparation Record be kept current, and that it contain specific information, including the dates and quantity of the investigational drug dispensed. It appears that you did not maintain any investigational drug accountability records with respect to the dispensing of (b)(4) and (b)(4). The dates and quantity of investigational drug used for each subject were not documented.

Failure to maintain adequate drug disposition records raises concerns about subject safety and data integrity. We acknowledge that your written response states that upon your discovery of both the lack of drug accountability and the missing vials, pharmacy and research SOPs were evaluated and revised; and that future studies at your site will be conducted under the umbrella of US Oncology Research, which has an electronic drug accountability system. However, as the clinical investigator, it was your responsibility to ensure that adequate records of the disposition of the drug were maintained; and US Oncology Research's policies, procedures, and activities do not negate your responsibility as the clinical investigator.

3. You failed to promptly report to the IRB all unanticipated problems involving risk to human subjects or others [21 CFR 312.66].

a. Subject 6002 was admitted to the hospital for bilateral deep venous thrombosis (DVT) and pulmonary embolism on (b)(4) and was discharged on (b)(4). You did not report this hospitalization to the IRB until 11/2/09.

b. Subject 6002 expired on **(b)(4)**, and you did not report this death to the IRB until 11/4/09.

Failure to report to the IRB unanticipated problems involving risks to subjects raises concerns about subject safety by undermining the IRB's role in continuing review and evaluating risks to subjects. We acknowledge that your written response states that future studies at your site will be conducted under the umbrella of US Oncology Research, and that with all US Oncology Research studies, unanticipated problems are reported to a project manager or safety specialist, who in turn reports the problem to the IRB. However, as the clinical investigator, it was your responsibility to ensure that unanticipated problems involving risks to human subjects or others were promptly reported to the IRB; and US Oncology Research's policies, procedures, and activities do not negate your responsibility as the clinical investigator.

4. You failed to obtain informed consent in accordance with the provisions of 21 CFR part 50 [21 CFR 312.60].

Your general responsibilities as a clinical investigator include obtaining the informed consent of each human subject to whom the drug is administered, in accordance with the provisions of 21 CFR part 50 [21 CFR 312.60]. 21 CFR 50.27 requires that informed consent be documented by the use of a written consent form approved by the IRB. However, on July 10, 2009, Subject 6002 signed an informed consent form that appears to be an informed consent template that was not approved by the IRB. At the top of each page of the form signed by Subject 6002, the form states, "Approvable Template MUST BE APPROVED FOR SITES BEFORE USE AS MODIFIED Oct 02, 2008." The IRB's May 12, 2009, Certificate of Approval for Protocol **(b)(4)** directed you, as the clinical investigator, to "[u]se only the most current consent form bearing the [IRB] 'APPROVED' stamp." Because the informed consent form signed by Subject 6002 did not bear this "APPROVED" stamp, and instead indicated that it was a template form not yet approved by the IRB, it appears that Subject 6002's informed consent was not documented by the use of a written consent form approved by the IRB.

Failure to obtain informed consent in accordance with the provisions of 21 CFR part 50 raises concerns about the extent to which subjects' rights, safety, and welfare were protected. We acknowledge that your written response states that future studies at your site will be conducted under the umbrella of US Oncology Research, and that the Clinical Trials Management System provided by US Oncology Research studies will only allow staff to print the most current informed consent form. Your response also states that all Clinical Research Coordinators will only print the informed consent form as needed for each patient from the Clinical Trials Management System, to ensure that the most up-to-date informed consent form is used. However, as the clinical investigator, it was your responsibility to ensure that informed consent was obtained in accordance with the provisions of 21 CFR part 50; and US Oncology Research's policies, procedures, and activities do not negate your responsibility as the clinical investigator.

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 adequately and promptly explain the violations noted above may result in regulatory action without further notice.

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 (formerly Lewin), M.D., M.P.H.
Branch Chief
Good Clinical Practice Enforcement Branch
Division of Good Clinical Practice Compliance