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## Inspections, Compliance, Enforcement, and Criminal Investigations

Linda D. Bosserman 7/19/11



Department of Health and Human Services

Public Health Service  
Food and Drug Administration

### WARNING LETTER

JUL 19, 2011

#### CERTIFIED MAIL RETURN RECEIPT REQUESTED

Linda D. Bosserman, M.D.  
Wilshire Oncology Medical Group, Inc.  
1502 Arrow Highway  
La Verne, CA 91750-5318

Ref: 11-HFD-45-07-01

Dear Dr. Bosserman:

Between December 8 and December 22, 2010, Ms. Carla J. Lundi, representing the U.S. Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of the following clinical investigations:

- Protocol (b)(4) of the investigational drug (b)(4), performed for (b)(4);
- Protocol (b)(4) of the investigational drug (b)(4), performed for (b)(4);
- Protocol (b)(4) of the investigational drug (b)(4), performed for (b)(4); and
- Protocol (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 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 January 10, 2011, written response to the Form FDA 483, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We are aware that at the conclusion of the inspection, Ms. Lundi presented and discussed the inspection observations on the Form FDA 483 with you. We wish to emphasize the following:

**1. You failed to ensure that the investigation was conducted according to the signed investigator statement, in that you failed to personally conduct or supervise the clinical investigation [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 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]. 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 Protocol (b)(4) and Protocol (b)(4) were 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, we note that your failure to adequately supervise a study coordinator for Protocol (b)(4) and Protocol (b)(4) led to problems with the conduct of these investigations as described below, which included failure to maintain adequate and accurate case histories, and failure to conduct assessments required by the protocols.

We note that in your January 10, 2011, response to the Form FDA 483, you state that the study coordinator who was delegated the tasks that led to the violations cited below, admitted her wrongdoing and resigned in February 2010. We also acknowledge that your response describes corrective and preventive actions that you have taken, including the appointment of a Director of Clinical Research with at least 8 hours per week designated to work on oversight of the clinical trials program, who will meet at least weekly with clinical trial coordinators and data managers. However, your response is inadequate because you have not submitted the revised standard operating procedures referenced in your January 10, 2011, response to the Form FDA 483, or specifically identified how changes in those procedures will serve to prevent the recurrence of this type of violation in the future. In your response to this letter, please provide this documentation. Without the submission of this information, the Agency is unable to undertake an informed evaluation of the potential use of your actions in preventing the recurrence of these violations. Moreover, as the investigator, it was your responsibility to ensure that Protocol (b)(4) and Protocol (b)(4) were conducted according to the signed investigator statements, and your failure to supervise your study coordinator led to the problems with these investigations described below.

**2. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].**

FDA regulations state that an investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data. Examples of your failure to maintain adequate and accurate case histories include, but are not limited to, the following:

a. Protocol (b)(4):

- The name and date of birth for Subject 107-380B were handwritten on a screening electrocardiogram (ECG) dated December 18, 2009. However, Subject 107-380B did not receive an ECG on December 18, 2009. Your records indicate that the ECG submitted on behalf of Subject 107-380B is identical to the ECG performed on December 6, 2009, for a research subject enrolled in a different clinical trial. This discrepancy in your records was acknowledged in your January 10, 2011, response to the Form FDA 483.
- Your records indicate that Subject 107-380B signed the informed consent form on November 25, 2009. However, this form was subsequently altered to reflect a re-consent date of December 14, 2009. This discrepancy in your records was acknowledged in your January 10, 2011 response to the Form FDA 483. We also note that, according to your January 10, 2011, response to the Form FDA 483 and your April 27, 2010, Note to File, after consulting with the sponsor's monitor, you explained the error to Subject 107-380B during the subject's February 24, 2010, follow-up visit, and the subject re-signed the informed consent form on that date.

These violations involve the records of one of the three subjects enrolled in Protocol (b)(4). Although the study coordinator admitted this wrongdoing and resigned from your practice, as the clinical investigator you maintain overall responsibility for the conduct of this clinical investigation. Your failure to maintain adequate and accurate case histories could potentially compromise the integrity of the data collected during the clinical investigation.

b. Protocol (b)(4):

- Case history records for Subject 089002 contain duplicate records with discrepant dates. Specifically, the Review of Inclusion & Exclusion Criteria form dated November 12, 2009, is a photocopy of the form dated November 5, 2009. The only difference between these two records is the altered date on the November 12, 2009, version.

According to your January 10, 2011, response to the Form FDA 483, this discrepancy occurred because inclusion/exclusion checklists were used as "working" documents, and the study coordinator was permitted to use your signature stamp on

study records. However, it was your responsibility as the investigator to ensure that adequate and accurate records were prepared and maintained, as required by 21 CFR 312.62(b). The discrepancy in the study records for Protocol **(b)(4)** represents an additional example of your failure to maintain adequate and accurate case histories, and could potentially compromise the integrity of the data collected during the clinical investigation.

We acknowledge that in your January 10, 2011, response to the Form FDA 483, you described your corrective and preventive actions taken in response to the above-listed violations. These actions include:

- the conduct of an investigation into the incidents of altered records;
- the resignation of the study coordinator who admitted to the alterations;
- the audit of the other clinical trials in which the study coordinator was involved;
- providing notice to the UCLA-TORI research network leadership, the study sponsor, and the IRB concerning your investigation, audit, findings, and corrective actions;
- providing training for your research staff on Standard Operating Procedures (SOPs) for clinical trials, Good Clinical Practices, and Human Subject Protection; and
- updating your SOPs with regard to signing inclusion/exclusion checklists and signing laboratory or diagnostic studies for subjects in clinical trials.

However, it was your responsibility as the investigator to ensure that adequate and accurate records were prepared and maintained, as required by 21 CFR 312.62(b). Furthermore, your response was inadequate in that you have not submitted your revised SOPs or specifically identified how changes in those procedures will serve to prevent the recurrence of these types of violations in the future. Without the submission of this information, the Agency is unable to undertake an informed evaluation of the potential use of your actions in preventing the recurrence of these violations.

Specifically, your January 10, 2011, response to the Form FDA 483 states that your "SOP dated 2/9/10 (Appendix J)" documents that physician signature stamps will no longer be used at your site. However, the document attached as Appendix J appears to be a Memo to File rather than an SOP. Furthermore, on page 8 of your response, in Item 8, you state that you have changed your SOPs with regard to signing off on laboratory and diagnostic studies for patients on clinical trials. However, this SOP has not been included in your response, and it is not clear how this SOP relates to the February 9, 2010, Memo to File. Because these two items are related to the signing of study records, your response to this letter should identify and appropriately document the relationship between the SOP identified in Item 8 of your response and the February 9, 2010, Memo to File, and should include documentation of these policies.

Your January 10, 2011, response to the Form FDA 483 also states that you now understand that all "working documents should have been pulled from [the] study documents[,] as they are not source documents." However, this response does not provide assurance that you will maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation, whether the documents are considered "working" documents or "source" documents. Item 7 on pages 7-8 of your response states that you instituted a policy in June 2010 that all internal inclusion/exclusion checklists will be completed and signed by an investigator. In your response to this letter, please submit documentation of this policy, as well as an explanation of how this policy and the new SOPs prevent the occurrence of violations similar to those listed above.

### **3. 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]. Protocol **(b)(4)** outlines the types and timing of required assessments in Section 6.3 and Table 2, Assessments During Study Treatment. You failed to ensure that Protocol **(b)(4)** was conducted according to the investigational plan in that you failed to ensure that all assessments required by Protocol **(b)(4)** were performed. Examples of your failure to follow the investigational plan include, but are not limited to, the following:

The following required assessments were not performed for Subject 089002:

- a. November 18, 2009 (Cycle 1, Day 1): Circulating tumor cells, pharmacokinetics, and pharmacogenomics;
- b. December 9, 2009 (Cycle 2, Day 1): Quality of Life FACT-O Questionnaire and circulating tumor cells; and
- c. December 30, 2009 (Cycle 3, Day 1): Quality of Life FACT-O Questionnaire.

We acknowledge that in your January 10, 2011, response to the Form FDA 483, you describe the corrective and preventive

actions taken in response to the above-listed violations. These corrective actions include:

- hiring additional staff;
- providing training for all your research staff on Standard Operating Procedures for clinical trials, Good Clinical Practices, and Human Subject Protection; and
- updating your Standard Operating Procedures.

However, as the clinical investigator, it was your responsibility to ensure that study-related procedures were performed in accordance with the protocol requirements. Failure to perform study-related procedures has the potential to jeopardize subject safety and welfare, and to compromise the interpretation and validity of the investigational endpoints. Although the assessments listed above are not the primary endpoints of the investigation according to the protocol, the conduct of the investigation and conformance to protocol must be taken as a whole. The inclusion of subjects who have been diagnosed with ovarian cancer in this study indicates that the collection of valid data on circulating tumor cells, pharmacokinetics, and pharmacogenomics is valuable for the complete evaluation of the study results. In addition, Protocol **(b)(4)** states that a secondary endpoint of the study is to assess health-related quality of life, thus indicating that valid quality-of-life data are necessary.

In addition, your response is inadequate in that you have not submitted the revised standard operating procedures referenced in your January 10, 2011, response to the Form FDA 483, or specifically identified how changes in those procedures will serve to prevent the recurrence of these types of violations in the future. In your response to this letter, please provide this documentation. Without the submission of this information, the Agency is unable to undertake an informed evaluation of the potential use of your actions in preventing the recurrence of these violations.

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  
Office of Scientific Investigations  
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Sincerely yours,  
/S/□  
Leslie K. Ball, M.D.  
Director (Acting)  
Office of Scientific Investigations  
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