Inspections, Compliance, Enforcement, and Criminal Investigations

Ratzan, Judith M.D. 2/16/11

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-45-02-04

R. Judith Ratzan, M.D.
1475 NW 12th Avenue
Miami, Florida 33136

Dear Dr. Ratzan:

Between July 19 and September 13, 2010, Mr. Craig Garmendia and Ms. Nicole Bell, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (Protocol **(b)(4)**, entitled **(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 and the documents submitted with that report, 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, Mr. Garmendia and Ms. Bell presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your response dated October 14, 2010, to Form FDA-483, but note that this response was received past the 15 working days from close of the inspection. Thus, while we have reviewed the response, we have not included a discussion of the response in this letter as per the Commissioner's Enforcement Initiative announced August 11, 2009. We wish to emphasize the following:

1. 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 trial, 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 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, you failed to adequately supervise the study staff to whom you delegated tasks. Many, if not all, of the other violations listed in this letter are traceable to your failure to adequately supervise staff and the

conduct of the investigation. For example, multiple episodes of chemotherapy misadministration occurred for 3 of 3 subjects enrolled, including administration of 6 cycles of an investigational drug to a subject after closure of the study. Adequate review of the chemotherapy orders could have prevented misadministrations, or at a minimum allowed you to discover flaws in your systems that led to repeated departures from the investigational protocol. Adequate supervision also could have prevented or minimized repeated failures to report adverse events and to conduct procedures required by the protocol. We note that your staff reported to Investigator Garmendia that you were not present at the clinical site for a majority of the study, and that you live outside of the State of Florida for six months of the year. It is apparent that procedures were not in place to compensate for your absence.

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

a. Our investigation revealed that for 3 out of 3 subjects, the administration schedule of chemotherapeutic agents was not conducted according to the investigational plan. We note the following examples:

i. Subject 4067803, who was randomized to Arm B, had multiple administration schedule deviations of either prescribed dose, infusion rate, or both:

Cycle/Date/Drug	Protocol Dose	Received Dose	Protocol IV Infusion Rate	Received IV Infusion Rate
1 on 11/19/08 **(b)(4)**	400 mg/m2	200 mg/m2		
2 on 12/3/08 **(b)(4)**			60 minutes for cycle 2	30 minutes
3 on 12/17/08 **(b)(4)**	85 mg/m2	100 mg/m2		
4 on 12/31/08 **(b)(4)**			2 hours	Boluspush
7 on 2/11/09 **(b)(4)**			2 hours	8 minutes

ii. Subject 2564977, who was randomized to Arm B, had multiple administration schedule deviations of either prescribed dose or infusion rate:

Cycle/Date/Drug	Protocol Dose	Received Dose	Protocol IV Infusion Rate	Received IV Infusion Rate
4 on 4/27/09 **(b)(4)**	400 mg/m2	320 mg/m2		
5 on 5/11/09 6 on 5/26/09 7 on 6/8/09 8 on 6/22/09 9 on 7/6/09 10 on 7/20/09	0mg/kg	5mg/kg		

Our investigation of Cycle 4 on April 27, 2009, for Subject 2564977 revealed that the **(b)(4)** was dosed at 320 mg/m2 instead of the protocol-required dose of 400 mg/m2. In the chemotherapy orders, it is noted that the subject's dose was modified due to diarrhea. However, in the chemotherapy administration notes from your clinic, the nurse's notes report that the subject had no complaints of diarrhea. Moreover, even if the subject did experience diarrhea, the protocol did not call for a reduction in **(b)(4)** dosage. Section 5.5.1 of the protocol, Chemotherapy Dose Modifications Arms A and B, outlines the required dose

reductions due to toxicity. That section of the protocol states, "Note that **(b)(4)** dose remains constant and without modification." Furthermore, the dose modification table in Section 5.5.1.1. of the protocol specifically instructs the clinical investigator to maintain dose levels for grades 1 and 2 diarrhea; to reduce both bolus **(b)(4)** and infusional **(b)(4)** one dose level for grade 3 diarrhea; and to reduce both bolus and infusional **(b)(4)** and **(b)(4)** by one dose level for grade 4 diarrhea.

Our investigation of Cycles 5-10 for Subject 2564977 identified the repeated misadministration of **(b)(4)** to Subject 2564977. You stated that you and your "study team did not have clarity in this case regarding the definition and intent of the sponsor upon study closure." However, after our review of the **(b)(4)** announcement dated April 29, 2009, closing the trial, we disagree with your statement. We note that the **(b)(4)** announcement clearly stated, "For patients currently being treated with the experimental regimen of **(b)(4)** in combination with **(b)(4)**, the **(b)(4)** must be discontinued…. Patients should continue on standard post-operative systemic therapy **(b)(4)** per protocol."

iii. Subject 4065381, who was randomized to Arm A (**(b)(4)**), had multiple administration schedule deviations of prescribed dose or infusion rate, as well as the wrongful administration of **(b)(4)**

Cycle/Date/Drug	Protocol Dose	Received Dose	Protocol IV Infusion Rate	Received IV Infusion Rate
3 on 12/3/08 **(b)(4)**	0 mg/kg	5 mg/kg		
4 on 12/17/08 **(b)(4)**	85 mg/m2	100 mg/m2		
4 on 12/17/08 **(b)(4)**			2 hours	12 minutes
6 on 1/14/09 **(b)(4)**			2 hours	5 minutes
9 on 2/25/09 **(b)(4)**			2 hours	5 minutes

b. Section 7.1 of the protocol, Therapeutic Parameters, outlines the timing of the required assessments. We note that 3 of 3 subjects enrolled did not have the required assessments performed.

i. Subject 4067803 did not have the following:

a. Urine Protein/Creatinine (UPC) ratio performed for Cycles 6, 9, and 12.
b. Carcinoembryonic Antigen (CEA) test was not performed for follow-up at the 9-, 15-, and 21-month visits.
c. History, physical, and **(b)(4)** performance status performed for Cycles 2, 4, 8, 9, and 11.
d. A 6 month follow-up visit.

ii. Subject 2564977 did not have the following:

a. UPC ratio performed for Cycles 1, 3, and 6.
b. CEA test was not performed for follow-up at the 9-, 12-, 15-, and 18-month visits.
c. History, physical, and **(b)(4)** performance status performed for Cycles 6 and 7, as well as the 15-month follow-up visit.
d. A 6-month follow-up visit.

iii. Subject 4065381 did not have the following:

a. History, physical, and **(b)(4)** performance status performed for Cycles 1, 2, 3, and 5.
b. A 6-month follow-up visit.

c. Section 5.3 of the protocol, Adverse Event Reporting Requirements, states, "Adverse events are reported in a routine manner at scheduled times during a trial…." We note that you failed to report the following adverse events to the sponsor in your CRFs for 3 of 3 subjects enrolled:

i. Subject 4065381: Cycle 3 (11/22/08 - 12/05/08): Nausea, Vomiting
ii. Subject 4067803:

a. Cycle 1 (11/19/08 - 12/02/08): Nausea
b. Cycle 2 (12/03/08 - 12/16/08): Dysuria, Joint Pain, Rectal Itching
c. Cycle 7 (02/11/09 - 02/24/09): Nausea
d. Cycle 9 (03/11/09 - 03/24/09): Hemoglobin (CTCAE Attribution), Leukocytes

iii. Subject 2564977

a. Cycle 3 (04/13/09 - 04/26/09): Dehydration, Diarrhea, Vomiting
b. Cycle 5 (05/11/09 - 05/25/09): Hyperlacrimation

Failure to perform study-related procedures and to administer chemotherapy regimens as required jeopardizes

subject safety and welfare, and compromises the interpretation and validity of the investigational endpoints.

3. 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)].

a. The Cycle 3 (11/22/08) Case Report Form (CRF) for Subject 4065381 documented the adverse event of Nail Change, yet no evidence was available in the source documents to support the event's occurrence.

b. All three study subjects had Case Report Forms (CRFs) in which the doses of **(b)(4)** bolus and **(b)(4)** infusion values were transposed. The value for **(b)(4)** infusion dose was incorrectly recorded in the **(b)(4)** bolus dose box, and the value for **(b)(4)** bolus was incorrectly recorded in the **(b)(4)** infusion. Furthermore, the **(b)(4)** bolus, which was recorded in the infusion box, was incorrectly converted from milligrams to grams. We also note that the dosing for **(b)(4)**, as noted in the source documents, is inconsistent with what was reported in the CRFs for the subjects and cycles, as noted in the table below.

Subject	Cycles(s)	Dose transposed	Incorrect unit label (gram)	Other
4065381 **(b)(4)** 52282	2-4,6, 9-11	yes	Yes	
	1	yes		
4067803 **(b)(4)** 52286	1,4,7	yes	Yes	
	2	yes	Yes	**b)(4)** dose was 183, but CRF says 138; **(b)(4)** dose was 483, but CRF says 274;**(b)(4)** dose was 860, but CRF says 648
	3	yes	Yes	
2564977 **(b)(4)** 52337	3,4,7-12	yes	Yes	**(b)(4)** bolus dose was 374, but CRF says 598; **(b)(4)** infusion dose was 1496, but CRF says 1870
	5,6	yes	Yes	

Failing to maintain adequate and accurate case histories compromises the interpretation and validity of the clinical investigational endpoints.

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 believe that your written response to the Form FDA 483 dated October 14, 2010, fully explains the actions you have taken to prevent similar violations in the future, please communicate that to us in writing within fifteen (15) business days. You may reference the written response dated October 14, 2010, in your response to this letter.

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 Branch I
Division of Scientific Investigations
Office of Compliance

Center for Drug Evaluation and Research
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Building 51, Room 5354
10903 New Hampshire Avenue
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Sincerely yours,

{See appended electronic signature page}

Leslie K. Ball, M.D.
Director
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
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signature.

/s/

LESLIE K BALL
02/16/2011

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