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## Inspections, Compliance, Enforcement, and Criminal Investigations

Weiner, Gilbert R. 7/14/14



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.: 14-HFD-45-07-0

Gilbert A. Weiner, D.O.  
**(b)(6)** [home address]

Dear Dr. Weiner:

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 September 23 and November 25, 2013. Ms. Brunilda Torres and Mr. Craig Garmendia, representing FDA, reviewed your conduct of a clinical investigation (Protocol **(b)(4)**, "**(b)(4)**") of the investigational drug **(b)(4)** (Sponsor: **(b)(4)**), which was purchased by **(b)(4)**, performed at the Miami Gardens clinical testing facility under the former Clinical Operations Division of Cetero Research.

We note that you served as the clinical investigator for Protocol **(b)(4)** from May 5, 2009, when you signed the Form FDA 1572, until April 12, 2010. The violations observed during the inspection occurred during the time that you were the clinical investigator.

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, Ms. Torres and Mr. Garmendia presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your December 3, 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 written response dated December 3, 2013, 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 failed to ensure that the investigation was conducted according to the investigational plan [21 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 hypersensitivity assessment forms be completed; that the investigator who evaluates adverse events not be involved in subject dosing; that subjects not be family members of study staff personnel; and that subject participation be terminated for any signs or symptoms of hypersensitivity after dosing of placebo on Day 1, but prior to dosing of double-blind trial medication on Day 8. You failed to adhere to these requirements. Specifically:

a. The protocol requires that all subjects receive a single-blind placebo dose on Day 1 and be evaluated for signs and/or symptoms of hypersensitivity to placebo on Days 1 and 2. In addition, the protocol requires that these evaluations be documented on each subject's hypersensitivity assessment form. During the inspection, we reviewed study records for 55 of the 129 randomized subjects and found that none had hypersensitivity assessment forms completed on Days 1 and 2. For example, Subjects 031, 032, 047, 256, 262, and 271 did not have hypersensitivity assessment forms completed on Days 1 and 2, as required by the protocol.

In your December 3, 2013, written response, you stated you did not have access to the study records and that you were therefore unable to review the information to explain why hypersensitivity assessments were not done for any of these 55 subjects. You also indicated that you did not recall that any of the assessments were not performed. However, on November 20, 2013, you met with the investigators to have a preliminary discussion of the inspection findings. During that meeting, **(b)(4)**, Associate Director of Global Clinical Compliance for **(b)(4)**, offered you copies of the study records, which you declined.

Your response is inadequate because you did not include any corrective actions that you, as a clinical investigator, have taken to prevent similar violations in the future.

b. The protocol requires that hypersensitivity assessment forms be completed on each dosing day (i.e., Days 1, 8, 36, and 78) and on the day following the dosing day (i.e., Days 2, 9, 37, and 79) for each subject. For each subject examined, you failed to complete the hypersensitivity assessment form for the day following the dosing day.

In your December 3, 2013, written response, you indicated that hypersensitivity assessments were continuously performed from the dosing until the day of discharge; that the hypersensitivity assessment forms were filled out after the first hour post-dose; and that any adverse reaction occurring after the form was filled out was captured as an adverse event. You also noted that upon subjects' discharge, you or your subinvestigator questioned and examined subjects to rule out any possible hypersensitivity reaction.

Your response is inadequate because you did not explain why the hypersensitivity assessment forms were not completed on the days following dosing days, and because you did not include any corrective actions that you, as a clinical investigator, have taken to prevent similar violations in the future.

c. The protocol provides that "[s]ubjects who are part of the study staff personnel or family members of the study staff personnel" will be excluded from entry into the study. A Protocol Deviation Form date June 20, 2010, indicated that Subject 037 was the cousin of a study staff member, and that Subject 004 was the son of a study staff member.

In your December 3, 2013, written response, you indicated that you were not able to review the inclusion/exclusion criteria information and that you did not recall issues regarding enrollment of relatives. Your response is inadequate because you did not provide a corrective action plan to prevent the recurrence of similar violations in the future.

Your failure to adhere to the investigational plan, including, for example, failure to complete hypersensitivity assessment forms, jeopardizes subject safety and welfare, and compromises integrity of the data collected at your site.

**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)].**

As a clinical investigator, you are 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 for Protocol **(b)(4)** include the hypersensitivity assessment forms, telemetry, and electrocardiograms. You have failed to maintain adequate and accurate case histories. Specifically:

- a. Signs and symptoms of hypersensitivity were not recorded on the hypersensitivity assessment forms for the following subjects:
  - i. For Subject 032, tachycardia, a sign of hypersensitivity, was reported on the adverse event form for Day 36, but was not reported on the hypersensitivity assessment form for Day 36.
  - ii. For Subject 057, nausea, a symptom of hypersensitivity, was reported on the adverse event form for Day 8, but was not reported on the hypersensitivity assessment form for Day 8.
  - iii. For Subject 227, tachycardia was reported on the adverse event form for Day 78, but was not reported on the hypersensitivity assessment form for Day 78.

In your December 3, 2013, written response, you indicated that subjects who experienced some tachycardia manifested this sign prior to dosing, and that their heart rates later returned to normal.

However, you did not provide documentation to show that Subjects 032 and 227 experienced tachycardia prior to dosing, and you did not explain why nausea was not documented in the hypersensitivity assessment form for Subject 057. Your response is also inadequate because you have not provided a corrective action plan to prevent the recurrence of similar violations in the future.

- b. Records corresponding to the listed subjects' dosing periods indicated that hypersensitivity assessment forms were completed, but those forms were missing, as follows:
  - i. Subject 002 – Periods 2 (Week 1) and 4 (Week 11)
  - ii. Subject 004 – Period 2 (Week 1)
  - iii. Subject 013 – Periods 1, 2, and 3 (Weeks 0, 1, and 5, respectively)
  - iv. Subject 014 – Periods 1 (Week 0) and 2 (Week 1)
  - v. Subject 015 – Periods 1 (Week 0) and 2 (Week 1)
  - vi. Subject 021 – Period 1 (Week 0)
  - vii. Subject 031 – Period 2 (Week 1)
  - viii. Subject 201 – Period 2 (Week 1)
  - ix. Subject 210 – Periods 2 (Week 1) and 3 (Week 5)
  - x. Subject 213 – Periods 1 (Week 0) and 2 (Week 1)
  - xi. Subject 214 – Periods 1 (Week 0) and 2 (Week 1)
  - xii. Subject 215 – Periods 1 (Week 0) and 2 (Week 1)

In your December 3, 2013, written response, you indicated that you were unable to review the above findings because you did not have access to the study records. You also indicated that it “does not appear logical to conduct the [hypersensitivity] assessments on some of the patients and only part or none on others.” Your response is inadequate because you did not provide an explanation for the missing study records, and because you did not provide a corrective action plan to prevent the recurrence of similar violations in the future.

- c. Study records contained hypersensitivity assessment forms that were signed and dated but that did not contain any subject identification or any other information with regard to hypersensitivity signs and symptoms. For example, study records contained hypersensitivity assessment forms with your dated signature but no other information for Days 36 and 78. In addition, for Subject 210, the hypersensitivity

assessment form for Day 36 contained your dated signature but was otherwise blank.

On September 9, 2013, you sent an e-mail to the sponsor noting that due to the large number of subjects, you signed and stamped the blank forms "just prior to filling them out."

In your December 3, 2013, written response, you indicated that you would stamp a block of hypersensitivity forms and indicated that you should have drawn a line across the signed, unused forms and initialed and dated them. You also stated that you plan to avoid this type of practice in future clinical trials. Please note, we expect that you will not pre-sign blank forms in FDA-regulated studies in the future.

d. Telemetry records were missing for at least 27 of the 38 subjects whose records were reviewed for inclusion of this record during the inspection.

e. Electrocardiograms were missing for Subjects 004 and 201.

We acknowledge that Items 2.d. and 2.e. above were not listed on the Form FDA 483 that was issued to you and, therefore, your written response to the Form FDA 483 did not address these violations.

Your failure to maintain adequate and accurate case histories, including the failure to record signs and symptoms of hypersensitivity and the failure to maintain telemetry records and electrocardiograms, compromises the validity and integrity of data captured at your site and raises concern about the adequacy of your protection of study subjects enrolled 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 actions 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. If you believe 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.  
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  
U.S. Food and Drug Administration  
Building 51, Room 5354  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

Sincerely yours,  
{See appended electronic signature page}

Sean Y. Kassim, Ph.D.  
Acting Director  
Office of Scientific Investigations  
Office of Compliance

Center for Drug Evaluation and Research  
U.S. Food and Drug Administration

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/s/

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SEAN Y KASSIM  
07/14/2014

Page Last Updated: 08/18/2014

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