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Inspections, Compliance, Enforcement, and Criminal Investigations

Horowitz, Jeffrey M.D. 3/21/11



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-45-03-02

Jeffrey Horowitz, M.D.
1030 President Avenue, Room 304
Fall River Nephrology
Fall River, MA 02720-5923

Dear Dr. Horowitz:

Between August 16, 2010, and September 3, 2010, Mr. Matthew Watson and Mr. Anthony Thomas,¹ 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, the documents submitted with that report, and your September 14, 2010, 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, Mr. Watson presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You failed to retain records required to be maintained under 21 CFR part 312 until 2 years after the investigation was discontinued and FDA was notified [21 CFR 312.62(c)].

On October 1, 2009, the sponsor discontinued your participation in Protocol **(b)(4)**. FDA was notified in a letter dated October 5, 2009, that your participation in Protocol **(b)(4)** was discontinued. As explained above, between August 16, 2010, and September 3, 2010, Mr. Watson and Mr. Thomas, representing FDA, conducted an inspection and met with you to review your conduct of Protocol **(b)(4)**. At the time of the inspection, which was less than two years after your investigation was discontinued and FDA was notified, the inspection revealed that you failed to retain the following records:

a. Electronic case report forms (eCRFs). During FDA's inspection, you stated that your study coordinator used a sponsor-provided laptop to enter data into the eCRF for each subject. You also stated that during the closeout visit conducted by the sponsor's monitor, the monitor took the sponsor-provided laptop computer containing the eCRFs. In your September 14, 2010, written response to Form FDA 483 (your written response), you further explained that the actual eCRF data disks were never obtained from the sponsor. However, it was your responsibility as the investigator to retain copies of the eCRFs for two years after the investigation was discontinued and FDA was notified [21 CFR 312.62(c)].

b. The Enrollment and Patient Status Log and the Screening/Enrollment Log. During FDA's inspection, your study coordinator obtained copies of these two logs from the sponsor. However, it was your responsibility as the investigator to retain copies of the logs for two years after the investigation was discontinued and FDA was notified [21 CFR 312.62(c)].

We acknowledge that in your written response you stated that you intend to "be more vigilant in documentation oversight than in the past." However, you did not specify the corrective actions you will take to address these violations or to prevent this type of violation from reoccurring in the future.

2. You failed 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 [21 CFR 312.62(b)].

FDA found discrepancies and deficiencies in records for both of the subjects enrolled in Protocol **(b)(4)**, which raises significant questions about the reliability of data at your site. Specifically:

a. The study flowsheets appear to document post-dialysis vital signs rather than pre-dialysis vital signs. The protocol required that vital-sign assessments, including body temperature, sitting blood pressure and sitting pulse measurements, be performed pre-dialysis at every visit. During FDA's inspection, your study coordinator stated that she transcribed vital-sign data from the dialysis center's Patient Treatment Records onto the study flowsheets, and then used the flowsheets to enter the data into the eCRFs. However, a comparison of the Patient Treatment Records and the flowsheets suggests that for some visits, your study coordinator recorded the post-dialysis vital-sign data on the study flowsheets rather than the pre-dialysis vital-sign data, as required by the protocol (see table below for examples). This discrepancy raises questions about the reliability of the data at your site, in part because the Study Coordinator used the flowsheets to enter data into the eCRFs.

Subject #	Visit #	Patient Treatment Record (pre-dialysis)	Patient Treatment Record (post-dialysis)	Study Flowsheet
00013	2 ² Washout Week 1	Sitting Blood Pressure (BP) 163/103 Body Temp 94.8°F Heart Rate (HR) 90	Standing BP 118/69 Body Temp 98.2°F HR 92	Sitting BP 118/69* Body Temp 98.2°F Sitting Pulse 92
	Visit #9	Sitting BP 127/94 Body Temp 96.4°F HR 93	Sitting BP 106/91 Body Temp 98.3°F HR 99	Sitting BP 106/91 Body Temp 98.3°F Sitting Pulse 99
00016	Screening	Sitting BP 150/68 Body Temp 97.5°F HR 59	Sitting BP 129/87 Body Temp 97.4°F HR 80	Sitting BP 129/87 Body Temp 97.4°F--pre 97.5°F** Sitting Pulse 80

Visit #5	Sitting BP 148/66 Body Temp 97.2°F HR 57	Sitting BP 164/87 Body Temp 97.4°F HR 58	Sitting BP 164/87 Body Temp 97.4°F HR 58
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* For Subject 00013's Washout Week 1 visit, the study coordinator appears to have recorded the post-dialysis *standing* blood pressure measurement on the flowsheet.

** For Subject 00016's Screening visit, the study coordinator appears to have recorded both the pre- and post-dialysis body temperatures on the flowsheet. Without a copy of the eCRF, we cannot determine whether the pre- or post-dialysis temperature was recorded in this subject's eCRF.

b. There are discrepancies between the Enrollment and Patient Status Log and the Screening/Enrollment Log referenced in 1.b. above. For example, the Enrollment and Patient Status Log for Subject 00013 shows March 2, 2009, as the date of informed consent; however, the Screening/Enrollment Log shows February 23, 2009, as the date of consent. Likewise for Subject 00016, the Enrollment and Patient Status Log shows March 9, 2009, as the date of informed consent; however, the Screening/Enrollment Log shows March 2, 2009, as the date of consent.

We note that in your written response, you stated that you intend to "be more vigilant in documentation oversight than in the past." 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, you did not specify the corrective actions you will take to address these violations or to prevent this type of violation from reoccurring in the future.

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

Section 7 of the protocol lists all of the required assessments in the protocol, and specifies when those assessments were to be performed. It appears that the following protocol-required assessments were not performed:

- a. For both subjects, there was no documentation showing that the blood pressure measurements were taken in accordance with the protocol. The protocol specified that each subject's blood pressure should be measured three times, and the mean of those three measurements should be used as the subject's blood pressure measurement, at every visit. There was no documentation to show that subjects' blood pressures were measured in accordance with these protocol requirements at any of the subjects' visits.
- b. For Subject 00016:
 - i. Laboratory Reports show that the protocol-required hematology test results were not calculated at Visits 4 (Baseline) and 8.
 - ii. There was no documentation available to show that the protocol-required laboratory evaluations were conducted at Visit 13.
- c. For Subject 00013:
 - i. There was no documentation available to show that the protocol-required physical examination was conducted at Visit 1 (Screening).
 - ii. There was no documentation available to show that the protocol-required laboratory evaluations were conducted at Visits 1 (Screening) and 4.

Failure to perform study-related assessments may jeopardize subjects' rights, safety, and welfare, and may compromise the reliability of the data at your site. Based on the documentation available at the time of the inspection, it appears that you did not ensure that these assessments were conducted in accordance with the protocol. It was your responsibility as the investigator to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

We acknowledge that it is possible that the eCRFs provide documentation that you measured blood pressure in accordance with the protocol, conducted the protocol-required laboratory evaluations at Visit 13 for Subject 00016, and conducted the protocol-required physical examination at Visit 1 and laboratory evaluations at Visits 1 and 4 for Subject 00013. However, as explained above, you failed to retain copies of the eCRFs in violation of 21 CFR 312.62(c). Moreover, to the extent that the eCRFs do not provide documentation that these assessments were conducted in accordance with the protocol, such deficiencies would suggest that, even if you conducted these assessments according to the protocol, you failed to prepare and maintain adequate and accurate case histories, as required by 21 CFR 312.62(b).

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

Each time the study drug was dispensed to a subject, the protocol required that the drug label be removed from the packaging and affixed to the Drug Label Form for that subject. However, the Drug Label Form for Subject 00013 did not include labels for the two drugs (medication randomization numbers³ 1010589 and 1020640) that, according to the Drug Accountability Log, were dispensed to the subject on May 22, 2009.

We note that in your written response, you stated that you "agree that there was [*sic*] inadequate drug dispensing records in the paperwork," but that you believed "it was better documented in the eCRF." However, it was your responsibility as the investigator to maintain adequate records of the disposition of the drug [21 CFR 312.62(a)]. As explained above, it was also your responsibility as the investigator to retain copies of the eCRFs for two years after the investigation was discontinued and FDA was notified [21 CFR 312.62(c)]. In addition, in your written response, you did not specify any corrective actions that you will take to address these violations or to prevent this type of violation from reoccurring 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 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 Branch I
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5354
10903 New Hampshire Avenue
Silver Spring, MD 20993

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

¹ Mr. Thomas was present at the inspection from August 16, 2010, through August 20, 2010.

² We note that on some of your study records, the number for this subject is recorded as "0013" instead of "00013."

³ On the drug labels affixed to the Drug Label Form, the medication randomization number was referred to as the "Med. #" On the Drug Accountability Log, this same number was referred to as the "Lot number."

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/s/

LESLIE K BALL
03/21/2011

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