Inspections, Compliance, Enforcement, and Criminal Investigations

Henry A Frazer, Pharm D, Clinical Investigator 6/5/13

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: 13-HFD-45-05-02

Henry A. Frazer, Pharm.D.
1758 Park Place, Suite 200
Montgomery, AL 36106-1134

Dear Dr. Frazer:

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 24 and October 3, 2012. Ms. Kimberly Dutzek, representing FDA, reviewed your conduct of the following clinical investigations:

- Protocol **(b)(4)**, "**(b)(4)**," of the investigational drug **(b)(4)**, performed for **(b)(4)**
- Protocol **(b)(4)**, "**(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 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 involved in those studies have been protected.

At the conclusion of the inspection, Ms. Dutzek presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your October 3, 2012, written response.

From our review of the establishment inspection report, the documents submitted with that report,and your October 3, 2012, written response, 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. You failed to adhere to these requirements. Specifically:

a. Protocol **(b)(4)** required that you dispense a handheld electronic device (LogPad) to subjects at Visit 2, prior to surgery, and that the subjects record their pain assessments in the LogPad during the study. You did not dispense a LogPad to Subject 09-006 at Visit 2 on March 4, 2011, because the subject was sedated and on a ventilator. In addition, five pain assessments for Subject 09-006 were entered into the LogPad by the study coordinator, rather than by the subject. During the inspection, your study coordinator indicated that she used the subject's login code and entered the subject's pain-assessment scores into the LogPad when the subject was unable to provide a pain score.

In your October 3, 2012, written response, you acknowledged that the LogPad was not dispensed to Subject 09-006 prior to surgery. You noted that after surgery, the subject was put on a "vent" (ventilator), was sedated, and was unable to participate in the evaluation of pain, via the LogPad or otherwise.

In your written response, you indicated that your study coordinator entered data directly into the LogPad, based on information she received either from the nursing staff or from study subjects. You indicated that your study coordinator entered pain scores "based on the staff nurses [*sic*] educated guess as to the pain level when the patient was obviously in pain as evidence of [*sic*] the patient's tossing and painful expressions on the patient's face." You also stated that "at times when the patient was either unwilling to complete the pain score or too disoriented to write into the diary or use the LogPad, [your study coordinator] asked the patient what her pain score was and entered that value onto the diary and added the patient's initials."

You indicated that by the time you became aware of this practice, your site had enrolled 8 subjects into the study, and all of them had completed the trial. You also indicated that the monitors challenged the validity of the pain data.

Your response is inadequate. Although you explained how the violation occurred, you failed to provide a corrective action plan to prevent recurrence of similar violations in the future.

Based on your written response, we have concerns that your study coordinator may have inappropriately entered data into the LogPad for other subjects, as well. We request that you inform us, in writing, of the extent to which pain-assessment data were not obtained directly from the subjects; the extent to which anyone other than the subjects entered pain-assessment data into LogPads; and how you intend to prevent the recurrence of similar violations in the future.

By failing to ensure that pain-assessment data were entered only by the subjects, as required by the protocol, you compromised the validity and integrity of data collected at your site.

b. Protocol **(b)(4)** required that subjects have an American Society of Anesthesiologists (ASA) Physical Status Classification of 1 to 3 and a QTc interval shorter than 450 milliseconds in order to be eligible for enrollment. Subject 09-006 did not meet these inclusion criteria. On March 4, 2011, the day of surgery, Subject 09-006 had an ASA Physical Status Classification of 4, which is defined as a patient with a severe systemic disease that is a constant threat to life. In addition, Subject 09-006 had a QTc interval of 453 milliseconds on the day of surgery. Consequently, Subject 09-006 was ineligible for Protocol **(b)(4)**.

In your October 3, 2012, written response, you failed to respond to Item 1.b. above. In addition, you failed to provide a corrective action plan to prevent recurrence of similar violations in the future.

Enrollment of subjects who do not meet eligibility criteria jeopardizes subject safety and welfare, and raises concerns about the validity and integrity of the data collected at your site.

c. Protocol **(b)(4)** prohibited the use of pain medications Percocet and Oxycontin (oxycodone hydrochloride) from Day 0 through completion of the trial.

1. From December 16 to December 18, 2010, Subject 31-003 received multiple doses of Percocet.

2. From March 4 to March 14, 2011, Subject 09-005 received multiple doses of oxycodone.

In your October 3, 2012, written response, you failed to respond to Item 1.c. above. In addition, you failed to provide a corrective action plan to prevent recurrence of similar violations in the future.

Your failure to prevent the administration and use of prohibited pain medications during the study compromised data integrity by prohibiting an evaluation of the therapeutic benefit of the study drug alone.

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)].

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. For Protocol **(b)(4)**, case histories include the data entered into the LogPads. You have failed to maintain adequate and accurate case histories. Specifically:

Protocol **(b)(4)** required that the subjects record their pain assessments in the LogPad during the study. For Subject 09-006, the LogPad contained assessments purportedly made and entered by the subject; however, five pain assessments were entered by the study coordinator and reflect the study coordinator's or nursing staff's assessments, rather than the subject's assessments.

During the inspection, your study coordinator indicated that she used the subject's login code and entered the subject's pain-assessment scores into the LogPad when the subject was unable to provide a pain score. In your October 3, 2012, written response, you noted that after surgery, the subject was put on a "vent" (ventilator), was sedated, and was unable to participate in the evaluation of pain, via the LogPad or otherwise.

In your written response, you also indicated that your study coordinator entered data directly into the LogPads, based on information received either from the nursing staff or from study subjects. You indicated that your study coordinator entered pain scores "based on the staff nurses [*sic*] educated guess as to the pain level when the patient was obviously in pain as evidence of [*sic*] the patient's tossing and painful expressions on the patient's face." You also stated that "at times when the patient was either unwilling to complete the pain score or too disoriented to write into the diary or use the LogPad, [your study coordinator] asked the patient what her pain score was and entered that value onto the diary and added the patient's initials."

You indicated that by the time you became aware of this practice, your site had enrolled 8 subjects into the study, and all of them had completed the trial. You also indicated that the monitors challenged the validity of the pain data.

Your response is inadequate. Although you explained how the violation occurred, you did not provide any information that would mitigate the violation's significant impact on data integrity, reliability, and validity. In addition, you failed to provide a corrective action plan to prevent recurrence of similar violations in the future.

Based on your written response, we have concerns that, in addition to Subject 09-006's records, other subjects' records may contain inaccurate data from the LogPads. We request that you inform us, in writing, of the extent to which subjects' records contain pain-assessment data that were not obtained directly from the subjects; the extent to which anyone other than the subjects entered pain-assessment data into LogPads; and how you intend to prevent the recurrence of similar violations in the future.

Your failure to maintain adequate and accurate case histories by failing to maintain adequate and accurate pain assessments compromised the validity and integrity of data captured 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 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
Food and Drug Administration
Building 51, Room 5354
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely yours,

{See appended electronic signature page}

Thomas N. Moreno, M.S.
Acting Director
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THOMAS N MORENO
06/05/2013

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