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Inspections, Compliance, Enforcement, and Criminal Investigations

McKay, Charles M.D.



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: 10-HFD-45-10-03

Charles McKay, M.D.
1124 West Carson Street, RB2
Torrance, CA 90502

Dear Dr. McKay:

Between February 24 and March 6, 2009, Ms. Diane Van Leeuwen and Ms. Trushani Shah, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation **(b)(4)** performed for **(b)(4)**

This inspection is a part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to 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, Ms. Van Leeuwen and Ms. Shah presented and discussed with you Form FDA 483, Inspectional Observations. 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 investigator statements (Form FDA 1572) for the above referenced clinical investigations, you agreed to take on the responsibilities of a clinical investigator at your site. Your general responsibilities include ensuring that the investigation 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). In the signed investigator agreement, you specifically agreed to personally conduct the clinical studies or to supervise those aspects of the studies that you did not personally conduct. While you may delegate certain study tasks to individuals qualified to perform them, as 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 clinical trials were conducted according to the signed investigator statement, the investigational plan, and applicable regulations, and in a manner that protected the rights, safety, and welfare of human subjects.

In our review of the inspection report and the documents submitted with that report, we find that you failed to have adequate involvement in and oversight of the study to ensure data integrity and to protect the rights, safety, and welfare of subjects enrolled in the study, as noted in Items 2 through 4 below.

In a written affidavit signed by you during the FDA inspection, you noted that you thought the training provided by the

monitors to you and your study coordinators was sufficient, and that if there were problems, the monitors would let you know. You further asserted that you did not know that you had to supervise the study and ensure that the study coordinators were correctly doing such things as completing source records and case report forms (CRFs), filling out adverse event and hospitalization forms, and notifying the IRB and sponsor on time. You also noted that it was not until the fall of 2008 that you became aware of the problems at your site, got involved in trying to identify usable data, and hired experienced people to help make improvements.

We wish to emphasize again that as the clinical investigator, it was your ultimate responsibility to ensure that the studies were conducted properly and in compliance with FDA regulations in order to protect the rights, safety, and welfare of study subjects.

2. You failed to promptly report to the IRB all changes in research activity [21 CFR 312.66].

Your site had been notified by the sponsor of several changes in the protocol during the time period when subjects were enrolled in the study. For example, the sponsor notified you of Protocol Amendment #2 in a letter dated July 20, 2007. In another letter, dated January 21, 2008, the sponsor reminded you to notify the IRB about Protocol Amendments #2 and #3. In addition, in a letter dated February 21, 2008, the sponsor notified you of Protocol Amendment #4. Finally, in a letter dated August 5, 2008, the sponsor notified you of Protocol Amendment #5. However, IRB records indicate that you failed to promptly report these changes. In several letters dated January 6, 2009, the IRB noted that it had not received notice of Protocol Amendments #2 through #5 until December 2008. Furthermore, by the time the IRB acknowledged receipt of these Protocol Amendments from you in December 2008, the study had already been closed at your site, as evidenced by a letter from the sponsor dated October 22, 2008.

In a written affidavit, you stated that with regard to Protocol Amendments #4 and #5, you were aware of the hazards of the use of **(b)(4)** and other drugs, as well as the risk of surgeries, as noted in the amendments. Thus, you had reviewed the subjects' charts and discussed these risks with the subjects to determine that they were not at risk. Per the affidavit, you noted that you did believe that the Protocol Amendments had been submitted to the IRB.

FDA's investigators were unable to find evidence that prior to the study being closed at your site, Protocol Amendments #2 through #5 were submitted to and approved by the IRB. Failure to submit these Protocol Amendments promptly to the IRB is a significant violation of FDA's regulations.

3. You failed to conduct the studies or ensure they were conducted according to the signed investigator statement and investigational plan [21 CFR 312.60].

a. The protocol defined a serious adverse event (SAE) as any adverse event (AE) that resulted in death, was immediately life-threatening, resulted in persistent or significant disability/incapacity, required or prolonged patient hospitalization, was a congenital anomaly/birth defect, or was deemed to be serious for any other reason representing a significant hazard. The protocol further stated that all AEs, serious and nonserious, were to be fully documented on the appropriate CRFs; and SAEs were to be reported to the sponsor using the Serious Adverse Event Report Form, with a documented causal relationship assessment and in as much detail as possible. Upon receipt of follow-up information, all remaining fields on the SAE form were to be completed or updated. Any serious or significant AE, whether or not it was thought to be related to the investigational product, and whether or not the investigational product had been administered, was to be reported immediately by telephone/fax to the sponsor. You failed to follow the protocol requirements. Examples include but were not limited to the following:

i. For Subject #001:

1. The subject had congestive heart failure that resulted in a hospitalization on **(b)(6)** Based on the FDA investigator's review of your source documents for this subject, it appears that this event was not documented on a Serious Adverse Event Report Form with a documented causal relationship assessment and was not reported to the sponsor until July 13 (no year documented) and again on November 12, 2008.

2. On August 7, 2007, your site was informed that this subject had suffered cardiac arrest, had been hospitalized, and was not doing well. In the FDA investigators' review of your source documents for this subject, there was no evidence that you informed the sponsor of this SAE. Subsequent to the subject's hospitalization, the subject died. Source records indicate that in September 2007 your site was aware of the subject's death. However, this additional SAE was not documented on the Serious Adverse Event Report Form with a documented causal relationship assessment, and was not reported to the sponsor until November 12, 2008.

ii. Subject #007 was hospitalized several times during the course of the study (on **(b)(4)** FDA's investigators were unable to find documentation that these events were reported to the sponsor.

b. The protocol specified that laboratory samples for safety analysis were to be collected and evaluated at the screening visit. FDA notes that the documentation reveals a significant delay in your review of four of seven subject records, such that subjects were either randomized into the study or had completed the study by the time you reviewed the protocol-required, screening-related documents. For example:

i. Documentation shows that you did not review the laboratory reports of samples taken at the screening visit on June

4, 2007, for Subject #002 until August 15, 2007. By the time you reviewed the source records, the subject had already been dispensed study drug (on June 11, 2007).

ii. Documentation shows that you did not review the laboratory reports of samples taken at the screening visit on November 1, 2007, for Subject #007 until November 9, 2007. By the time you reviewed the lab report, the subject had been randomized into the study and had been dispensed study medication (on November 8, 2007).

c. The protocol specified that at the screening visit (i.e., Visit 1), key baseline characteristics were to be recorded, including demographics, medical history, physical exam, and vital signs.

i. For Subject #002, there was no documentation that a physical examination was performed at the screening visit, and only limited information is documented in the subject's medical history.

ii. Subject #007's physical examination was not conducted until after the subject was randomized into the study. The subject's physical examination was performed on December 6, 2007, which was after the screening visit (on October 29, 2007) and after the subject had been randomized into the study and dispensed study drug (on November 8, 2007).

d. The protocol specified that during the study, the patients were to return to the clinic for regularly scheduled follow-up visits (at 1, 3, 6, 9, and 12 months from randomization) and then every 4 months for the duration of the trial, as specified in the protocol flow chart, to assess study medication compliance and accountability, concomitant therapy or intervention, and conduct of efficacy and safety-related assessments. Furthermore, the protocol required that all randomized patients be followed through to the final follow-up visit in accordance with the schedule established at the time of randomization, regardless of treatment status (i.e., permanent or temporary discontinuation). The following subjects were not adequately followed per the protocol:

i. For Subject #002, records indicate that after Visit 6 (on December 6, 2007), your site staff did not see the subject for the 9-, 12-, and 16-month post randomization visits. Your site staff did not conduct any protocol-required visits for this subject again until the subject was terminated from the study on November 21, 2008.

ii. For Subject #004, records indicate that after the 3-month post-randomization visit on October 16, 2007, your site staff did not see the subject for the 6-, 9-, and 12-month post-randomization visits. You did not see this subject again until October 16, 2008.

iii. For Subject #005, the 12-month post-randomization visit occurred two months later than prescribed by the protocol.

iv. For Subject #007, after the 3-month post-randomization visit in February 2008, your site staff did not see the subject for the 6- and 9-month post randomization visits. You did not see this subject again until October 10, 2008.

Given the length of time between clinic visits, we are unsure how you adequately protected the rights, safety, and welfare of the subjects enrolled into the study.

e. The protocol required that laboratory sampling to include International Normalized Ratio (INR) testing be done at least every four weeks, and that hepatic tests be done monthly. For the following subjects, laboratory testing was not performed as specified in the protocol:

i. For Subject #002, records indicate that after March 20, 2008, there were no monthly INR tests conducted on this subject. In addition, no documentation was found that monthly hepatic tests were performed on this subject between Visit 6 (on December 6, 2007) and the time the subject terminated from the study on November 21, 2008.

ii. For Subject #004, no evidence was found that monthly hepatic function tests were performed after October 16, 2007, to the time the subject terminated from the study on October 24, 2008.

iii. For Subject #007, no evidence was found that monthly hepatic function tests were performed after February 3, 2008, to the time the subject terminated from the study on October 24, 2008.

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)].

FDA's investigation found that you failed to maintain adequate records of the disposition of the drug for all five subjects randomized in the study.

a. Subject #001 was dispensed study medication on March 23, 2007. Records contained no information concerning the quantity of study drug used by this subject.

b. For Subject #002, records were discrepant concerning the dates on which the subject was dispensed study medication, and the quantities dispensed. Per the dispensing/returning log, the subject was dispensed study drug on June 11, 2007; August 10, 2007; and December 6, 2007, none of which were returned. Per the study medication dispensation report, the subject was dispensed study drug on June 11, 2007; September 7, 2007; and December 6, 2007. In addition, per the dispensing/returning log, the subject was dispensed only 1 bottle of drug on June 11, 2007; however, the study medication dispensation report shows that the subject was dispensed 3 bottles of study

drug, each from a different record kit number.

c. For Subject #004, records contained no information related to the quantity of drug used by the subject at the 3-month follow-up visit. There was also no information concerning the dates on which the investigational drugs that had been dispensed on July 13, 2007; October 16, 2007; and December 12, 2007, were returned to the site. In addition, the information related to the dispensation of study drugs on December 12, 2007, was "estimated" and was not filled out until December 11, 2008, after the subject was terminated from the study (on October 24, 2008).

d. For Subject #005, records contained no information related to the quantity of study drug used by the subject after dispensation of the study drug on August 3, 2007 (randomization visit) and on December 3, 2007 (3-month post randomization visit). In addition, 6 bottles of drug were dispensed on some unknown date after December 2007 and were returned to your site empty on October 10, 2008. Records did not specify when the bottles were dispensed or the quantity of study drug used by the subject.

e. For Subject #007, records contained no information related to the quantity of study drug used by the subject after dispensation of the study drug on November 8, 2007 (randomization visit) and on February 15, 2008 (3-month post-randomization visit).

f. Source records indicate that 2 bottles of **(b)(4)** and 6 bottles of **(b)(4)** were missing from the total drug inventory at your site.

Your failure to maintain adequate and accurate drug disposition records raises concerns regarding adequate disposition of randomized drug to subjects, and calls into question the integrity of the data collected.

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 Lewin, M.D., M.P.H., at 301-796-3397; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

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Sincerely yours,
{See appended electronic signature page}
Leslie K. Ball, M.D.
Director
Division of Scientific Investigations
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/s/

LESLIE K BALL
10/23/2009

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