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Inspections, Compliance, Enforcement, and Criminal Investigations

Picus, Dr. Joel



Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Joel Picus, M.D.
Washington University of St. Louis
660 South Euclid, Box 8056
St. Louis, MO 63110

Ref: 10-HFD-45-09-02

Dear Dr. Picus:

Between October 14 and 28, 2009, Ms. Kathleen Swat, representing the Food and Drug Administration (FDA), conducted an investigation and met with you, to review your conduct of the following clinical investigations:

Protocol **(b)(4)**, entitled **(b)(4)** of the investigational drug **(b)(4)**, performed for **(b)(4)**.

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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 and the protection of human subjects. We are aware that at the conclusion of the inspection, Ms. Swat presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your responses dated November 11, 2009, and January 6, 2010, to Form FDA-483. 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 trials, 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 a 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 protected the rights, safety, and welfare of human subjects. Your failure to adequately supervise led to significant problems with the conduct of the study described below.

2. You failed to ensure that the investigation was conducted according to the investigational plan, and you failed to protect the rights, safety, and welfare of the subjects under your care [21 CFR 312.60].

As the clinical investigator, you are responsible for ensuring that the investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations, and for protecting the rights, safety, and welfare of study subjects. Failure to adhere to protocol-specified procedures compromises the safety and welfare of subjects enrolled in the clinical investigation. Specifically:

a. Protocol **(b)(4)** specified that blood samples for chemistry and hematology should be drawn and the test results should be reviewed within the 24 hours prior to dose administration. The protocol further specified that Liver Function Test (LFT) results must be reviewed for dose modification and withholding of treatment.

Our investigation found no documentation that Subject 040-001's LFT results were reviewed by you or your research staff for the protocol-specified procedures for dose modification and withholding treatment, and the subject was dosed on April 3, 2009.

On **(b)(4)**, Subject 040-001 was taken for emergency medical care with symptoms of vomiting and fever. Subject 040-001 was pronounced dead on **(b)(4)**, by the attending physician, with the cause of death being attributed to cardiac arrest due to severe metabolic acidosis due to multiorgan failure.

In a follow-up case report form dated October 7, 2009, you reported that Subject 040-001 died of liver failure. You reported that the death was not due to a gastrointestinal stromal tumor (GIST), and that the relationship of the death to the study drug was "probable." You also documented the protocol deviation that Subject 040-001 was treated on April 3, 2009, with elevated LFT, although the protocol specified that the dose should have been withheld.

b. Protocol **(b)(4)** specified that study drugs were to be prepared by the pharmacist or designee who was trained in the safe handling and administration of a cytotoxic agent.

The Infusion Preparation Log for Subject 040-001 documents that study drugs were prepared on March 24, March 27, March 31, and April 3, 2009, by an individual identified only by the initials **(b)(6)**. There was no documentation in the study records that **(b)(6)** was the pharmacist or designee, or that **(b)(6)** had been trained in the safe handling and/or administration of a cytotoxic agent.

In your response dated November 11, 2009, you acknowledge that a number of procedures were not appropriately followed, that the abnormal laboratory results were not reviewed by staff prior to treatment, and that the study drug was not withheld as the protocol specified. Further, you indicated that you failed to maintain an accurate Delegation of Authority log that identified **(b)(6)** and the responsibilities delegated to **(b)(6)**.

We acknowledge your response that you have implemented a formal double check process that requires proof that one registered nurse (RN) documents his/her review of the laboratory values and that a second RN documents a separate and independent review, prior to the Pharmacy dispensing study medications. Your response is acknowledged and is acceptable if implemented as proposed. In addition, you further indicated that you are revising staffing, so that all matters pertaining to studies will be performed by a restricted subset of trained research staff members. We acknowledge your response. However, we are concerned that the response is not adequate to prevent future recurrence of the violation noted above.

3. You failed to obtain informed consent in accordance with the provisions of 21 CFR Part 50 [21 CFR 312.60].

Except as provided in 21 CFR 50.23 and 21 CFR 50.24, no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative [21 CFR 50.20]. Informed consent must be documented by the use of

a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent [21 CFR 50.27(a)].

For Protocol **(b)(4)**, Subject 040-001's screening date was reported as March 19, 2009. The subject signed the IRB-approved informed consent on March 24, 2009. However, source records for Subject 040-001 document that study-related tests and procedures were performed prior to the date of consent. A blood sample was collected for study screening on March 12, 2009; the investigational dose was prescribed on March 20, 2009; and subject randomization occurred on March 23, 2009. Study-qualifying electrocardiograms (ECG), an eye examination, and a blood draw were performed on March 23, 2009.

In your response dated November 11, 2009, you acknowledge that you failed to obtain written consent from the subject prior to conducting all screening procedures, but that you documented the subject's verbal consent process in study records. The regulations require that informed consent be signed and dated by the subject or the subject's legal representative prior to the subject's involvement in the investigation [21 CFR 50.20]. Failing to obtain adequate informed consent jeopardizes the safety and welfare of enrolled subjects by denying them an opportunity to assess the risks and benefits of their participation in the clinical investigation.

We acknowledge your response. However, the response is not adequate, because you did not propose corrective actions to prevent future recurrence of the violation noted above. In particular, your response did not indicate that you properly understand the regulations for obtaining the legally effective informed consent of the subject.

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)].

Drug accountability records are incomplete and inaccurate for Protocol **(b)(4)**. There are discrepancies in dates, lot numbers, and drug identification numbers. Examples include but are not limited to the following:

- a. Master Investigational Product Accountability Records do not account for all study drug received on September 29, 2009. Kits 754083, 765462 and 842798 listed on the Proof of Receipt record were not documented in the Master Investigational Product Accountability Record.
- b. Investigational drug received on October 07, 2009, boxes 00690997 and 00696204, are documented twice in the Drug Accountability Records.
- c. Subject Specific Investigational Product Accountability Records for Subject 6111-08201 lack complete documentation for IV Bag Size, Total Volume Prepared, and Number of IV Bags Used.

We note your acknowledgment that you failed to maintain adequate and accurate drug accountability records.

We also acknowledge the corrective actions, described in your written response, that you have taken to prevent drug accountability discrepancies in the future. We find these corrective actions adequate, if implemented as proposed.

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:

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Sincerely yours,

/S/

Leslie K. Ball, M.D.

Director

Division of Scientific Investigations

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