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Inspections, Compliance, Enforcement, and Criminal Investigations

George C. Velmahos, M.D., Ph.D 11/29/13



Department of Health and Human Services

Public Health Service
Food and Drug Administration
Center for Biologics Evaluation
and Research
1401 Rockville Pike
Rockville, MD 20852-1448

November 29, 2013

By Overnight Delivery and Facsimile Transmission

CBER-14-0

Warning Letter

George C. Velmahos, M.D., Ph.D.
Division of Trauma, Emergency Surgery, and Surgical Critical Care
Massachusetts General Hospital
165 Cambridge Street, Suite 810
Boston, Massachusetts 02114

Dear Dr. Velmahos:

This letter describes the results of a Food and Drug Administration (FDA) inspection that concluded on July 25, 2013. An FDA investigator met with your staff to review your conduct of a clinical study entitled **(b)(4)**. The FDA conducted this inspection under the Bioresearch Monitoring Program, which includes inspections designed to review the conduct of research involving investigational drugs.

At the end of the inspection a Form FDA 483, Inspectional Observations, was issued and discussed with you. We received and reviewed your letter dated August 2, 2013 ("Response Letter") in response to the Form FDA 483.

Based on our evaluation of the evidence obtained by the FDA, we have determined that you violated regulations governing the proper conduct of clinical studies involving investigational new drugs, as published in Title 21, *Code of Federal Regulations* (CFR) Part 312 (available at <http://www.gpoaccess.gov/cfr/index.html>). The applicable provisions of the CFR are cited for each violation listed below.

1. You failed to ensure that the investigation was conducted according to the signed

investigator statement, the investigational plan, and the applicable regulations, and to protect the rights, safety, and welfare of subjects under your care. [21 CFR § 312.60].

A. **(b)(4)**

Subject	Dose	Outcome
(b)(6) (b)(4)		(b)(4)
(b)(6) (b)(4)		(b)(4)
(b)(6) (b)(4)		(b)(4)
(b)(6) (b)(4)		(b)(4)

By administering an incorrect dose to each of the patients above, you failed to ensure that the investigation was conducted according to the investigative plan. Your Response Letter did not provide an explanation for the incorrect dose administration. Please provide a written response.

B. **(b)(4)**

- i. **(b)(4)**
- ii. **(b)(4)**

Your Response Letter did not explain why **(b)(4)** was ordered prior to randomization. Please provide a written response.

C. Informed consent was obtained from Subjects **(b)(6)** by physicians not included on the signed Form FDA 1572.

Your Response Letter explained that you will conduct a review of study-related personnel ever six months and that Delegation of Authority Logs will be used as a master list of staff to track personnel involvement. We accept your explanation and remind you that the Form FDA 1572 should be promptly updated to accurately reflect all changes to study personnel.

D. You failed to comply with the investigational plan in that source documentation was inadequate according to protocol section 11.1. Protocol section 11.1, Source Data and Records, requires that "For each subject enrolled, the investigator will indicate in the source record(s) that the subject participates in this study...The investigator will record the following specific data which are not part of routine documentation in the patient's file: study identification code (**(b)(4)**), patient number in the study, investigational drug details (including amount and batch number, dates of administration), any AE occurring during course of the study, laboratory test results obtained locally, time and reason for premature withdrawal, if appropriate." The inspection revealed that subject source records did not include documentation of the study as required by protocol section 11.1.

In your Response Letter, you acknowledge that the collection of source documentation may not have been optimal. Corrective actions implemented to improve collection of source documentation include, but are not limited to, a review of current projects; instructions to staff to ensure that source documentation is available to support CRF entries; repeated announcements at weekly meetings regarding source documentation of the informed consent process, study drug **(b)(4)**, dosing, termination, and long term follow-up; and additional training. Your corrective actions are acceptable if they are properly implemented.

2. You failed to administer the drug only to subjects under the investigator's personal supervision or under the supervision of a subinvestigator responsible to the investigator. [21 C.F.R. § 312.61].

Personnel not included on the signed Form FDA 1572, which lists subinvestigators who will assist in the conduct of the investigation, or on the Site Responsibility Log issued orders for **(b)(4)** of the

study drug to study subjects. These personnel ordered study drugs for **(b)(4)** subjects.

During the inspection, you explained that the Attending Physician does not write orders. You explained that orders are written by surgical residents. This practice constitutes a failure to administer a study drug only to subjects under the investigator's personal supervision or under the supervision of a subinvestigator responsible to the investigator.

Your Response Letter did not explain why personnel not included on the signed Form FDA 1572 or the Site Responsibility Log issued orders for **(b)(4)** of the study drug to study subjects. Please provide a written response.

3. You failed to prepare and maintain adequate and accurate case histories that recorded all observations and other data pertinent to the investigation on each individual administered the investigational drug. Case histories include case report forms and supporting data. [21 CFR § 312.62(b)].

A. Supporting data and documentation were missing from or did not match CRFs in numerous instances. In particular, subject weight either was not recorded in source documentation or did not match the subject weight recorded in the CRF for **(b)(4)** subjects.

During the inspection, you explained that there were no bed scales in the Emergency Department and, as a result, subject weight was estimated, self-reported, or not recorded. Your Response Letter explains that routine recording of patient weight and height was implemented in April 2013, and that, in the future, you will ensure documentation of weight for weight-based dosing studies. Your corrective actions are acceptable if they are properly implemented.

B. Source documentation was inadequate to capture adequate and accurate case histories for subjects.

i. Source data, including **(b)(4)** times, vital signs, and weight for the majority of subjects, was captured on loose leaf paper maintained in the CRF binder. This source data was unattributable and incomplete. Your Response Letter failed to provide an explanation for this incomplete supporting data. Please provide a written response.

ii. The inspection revealed that source documentation was inadequate to show that subjects were contacted and/or scheduled to complete the protocol-required 21 day, 3 month and 6 month follow-up visit, resulting in failure to capture and document adverse events.

In your Response Letter, you acknowledge that long-term follow-up (after the patient's discharge from the hospital) to six months was inconsistent. Although follow-up was inconsistent, you explain that you expect that no major adverse events were missed because your clinical operations system is a closed one, in that patient care providers refer almost exclusively within the system and patients return almost exclusively to physicians within the system. You expect that subjects experiencing serious adverse events would be managed within your hospital system, and that you would have been notified of the adverse events or possibly involved in the care of these subjects.

In your Response Letter, you acknowledge that the collection of source documentation may not have been optimal. Corrective actions implemented overall to improve collection of source documentation include, but are not limited to, a review of current projects; instructions to staff to ensure that source documentation is available to support CRF entries; repeated announcements at weekly meetings regarding source documentation of the informed consent process, study drug **(b)(4)**, dosing, termination, and long term follow-up; and additional training. Your corrective actions are acceptable if they are properly implemented.

4. You failed to obtain the informed consent of each human subject to whom the drug was administered in accordance with the provisions of 21 CFR Part 50. [21 CFR § 312.60].

A. No documentation was located during the inspection to show that informed consent was obtained from Subject **(b)(6)**

In your Response Letter, you acknowledge that the informed consent for Subject **(b)(6)** is missing. You implemented new procedures to document the informed consent process and verify that the signed documents are properly filed, The corrective actions described in your Response Letter are acceptable if they are properly implemented.

B. An outdated informed consent document was used to obtain informed consent from Subjects **(b)(6)**. Subject **(b)(6)** signed a version of the consent form on June 3, 2010, that had expired on May 28, 2010. Subject **(b)(6)** signed a version of the consent form on July 29, 2010, that had expired on May 28, 2010.

In your Response Letter, you explain that you have reviewed all informed consent forms currently in use to ensure that all are current, and that you developed checklists to confirm that the current forms are being used. Your corrective actions are acceptable if they are properly implemented.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of this investigational product. It is your responsibility to ensure adherence to each requirement of the law and relevant regulations.

In your Response Letter, you describe corrective actions implemented to address the inspectional findings. We request that you provide the additional information requested in this letter.

Within fifteen (15) business days of receipt of this letter, please provide such written documentation of the actions you will take to correct these violations and prevent the recurrence of similar violation in current and future studies for which you are the clinical investigator. Specifically, please provide the additional information requested in this letter. Failure to respond to this letter and to take appropriate corrective action could result in FDA taking regulatory action without further notice to you. For instance, FDA could initiate disqualification proceedings against you in accordance with 21 CFR 312.70. If you do not believe you are in violation of FDA requirements, include your reasoning and any supporting information for our consideration.

Please send your written response to:

Christine Drabick
Division of Inspections and Surveillance (HFM-664)
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
1401 Rockville Pike, Suite 200N
Rockville, Maryland 20852-1488
Telephone: 301-827-6323

We also request that you send a copy of your response to the FDA District Office listed below.

Sincerely,

/S/

Mary A. Malarkey, Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

cc: CAPT Mutahar Shamsi, District Director
Food and Drug Administration
One Montvale Avenue, Fourth Floor
Stoneham, Massachusetts, 02180

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