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**Inspections, Compliance, Enforcement, and Criminal Investigations**

**Janet K Tillisch, MD 6/20/13**



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

June 20, 2013

By Overnight Delivery and Facsimile Transmission

CBER-13-03

### **Warning Letter**

Janet K. Tillisch, M.D.  
1702 South University Drive  
Fargo, North Dakota 58103

Dear Dr. Tillisch:

This letter describes the results of a Food and Drug Administration (FDA) inspection that concluded on April 9, 2013. The FDA investigators met with you to review your conduct of the following clinical studies:

**(b)(4)**

**(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 April 24, 2013 ("Response Letter"), in response to the Form FDA 483.

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 fulfill the general responsibilities of an investigator. [21 CFR § 312.60 and Part 50].**

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and, for the control of drugs under investigation. When you signed the investigator statement (Form FDA 1572) for the above-referenced clinical investigations on May 16, 2011, 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, such delegation requires adequate supervision of those to whom you delegate authority. You are responsible for the oversight of study personnel and for reviewing the work of study personnel to ensure that they follow the investigational plan and procedures.

Our investigation indicates that you delegated to the Site Management Organization (SMO), **(b)(4)** the conduct of the study visits and the completion of study records for such visits, including Case Report Forms (CRFs). There is no evidence that you adequately oversaw and reviewed the study activities you delegated to **(b)(4)**. As described below, it appears that you failed to review study records generated by **(b)(4)** with reasonable care, including by failing to ensure that you had access to certain source documents while the studies were ongoing. Your lack of supervision and personal involvement resulted in failure to ensure that the study was conducted according to the signed investigator statement, the investigational plan, and applicable regulations.

A. Based on the available information, it appears that, while the studies were ongoing, you did not have access to certain source records ("electronic diaries" or "e-diaries") in which subjects recorded adverse event information and other observations pertinent to the subject's case history. As a result, you placed subjects at risk because you did not promptly review and evaluate adverse events to determine their seriousness and relationship to the investigational product, and to perform any necessary medical intervention. In addition, as described below in item 2, you failed to ensure that adverse events were recorded in CRFs as required by the protocol.

In your Response Letter you explain that you were issued a password to access the e-diaries. Please explain when you received access to the e-diaries and when the e-diaries were accessible to you for review.

B. As described below in item 3, multiple study records, including CRFs, were incomplete or missing.

In your Response Letter you explain that **(b)(4)** managed key aspects of your clinical trials, including clinical study coordination and recordkeeping. You further explain that **(b)(4)** abruptly closed in August 2012 and did not provide you with documentation or information for any of the trials they managed. As noted above, while you may delegate certain study tasks to individuals qualified to perform them, such delegation requires adequate supervision. Had you, as the clinical investigator, reviewed the study records with reasonable care, these recordkeeping deficiencies would have been obvious to you.

**2. You failed to ensure that the investigation was conducted according to the signed investigator statement, the investigational plan, and the applicable regulations in order to protect the rights, safety, and welfare of subjects under your care. [21 CFR § 312.60].**

A. The following adverse events were recorded in the subjects' e-diaries but were not reported in the Adverse Event Log of the CRFs as required by section 9.12.2 of the protocol for Study **(b)(4)**

- i. **(b)(4), (b)(6)**
- ii. **(b)(4), (b)(6)**
- iii. **(b)(4), (b)(6)**

iv. **(b)(4), (b)(6)**

B. Section 7.8 of the protocol for Study **(b)(4)** requires that an effort must be made to determine why subjects failed to return for the necessary visits and that information detailing why a subject fails to return for the necessary visits or is discontinued from the study, as well as the date of withdrawal, will be recorded on the study outcome CRF. This requirement was not met for the following two subjects:

i. **(b)(4), (b)(6)**

ii. **(b)(4), (b)(6)**

In your Response Letter you did not address these findings. Please provide a written response.

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

A. **(b)(4), (b)(6)**

In your Response Letter you did not address this finding. Please provide a written response.

B. The following recordkeeping deficiencies were observed during the inspection:

**STUDY (b)(4)**

i. **(b)(4), (b)(6)**

ii. **(b)(4), (b)(6)**

iii. **(b)(4), (b)(6)**

In your Response Letter you did not address these findings. Please provide a written response.

**STUDY (b)(4)**

iv. **(b)(4), (b)(6)**

v. **(b)(4), (b)(6)**

a. **(b)(4), (b)(6)**

b. **(b)(4), (b)(6)**

In your Response Letter you did not address this finding. Please provide a written response.

vi. **(b)(4), (b)(6)**

a. **(b)(4), (b)(6)**

b. **(b)(4), (b)(6)**

c. **(b)(4), (b)(6)**

Items vi. a. and b. were not addressed in your Response Letter. Item vi. c. was not on the Form FDA 483. Please provide a written response to items vi. a-c.

**STUDIES (b)(4)**

vii. Multiple CRFs contained an incorrect header showing the name and site number of another investigator.

In your Response Letter you acknowledge that certain CRFs had incorrect headers. You explain that the headers were later corrected by Essentia Health staff during the internal review of the study, after notification of the **(b)(4)** closure. You further explain that the headers corrected by Essentia Health staff were not dated, timed, or initialed and the staff who made the corrections are no longer available to be contacted.

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

In your Response Letter you describe corrective actions to address both the **(b)(4)** closure and the conduct of research studies in general. We request that you provide the additional information requested in this letter.

Within fifteen (15) business days of receipt of this letter, please provide written documentation of the actions you will take to correct these violations and prevent the recurrence of similar violations in current and future studies for which you are the clinical investigator. 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: Michael Dutcher, District Director  
Food and Drug Administration  
250 Marquette Avenue, Suite 600  
Minneapolis, Minnesota 55401

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