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## Inspections, Compliance, Enforcement, and Criminal Investigations

Cohen, Yale M.D. 8/12/11



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: 11-HFD-45-08-01

Yale Cohen, M.D.  
3702 Washington Street, Suite 401  
Hollywood, FL 33021

Dear Dr. Cohen:

Between February 7 and February 11, 2011, Ms. Barbara Wright and Ms. Teresa Navas, representing the U.S. Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (Protocol **(b)(4)**, titled "**(b)(4)**") of the investigational drug **(b)(4)**, performed for **(b)(4)**. This letter requests prompt corrective action to address the violations cited, some of which are recurrences or continuations of observations noted in the letter FDA sent to you on October 8, 2009.

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, the documents submitted with that report, and your written response dated February 28, 2011, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. At the conclusion of the inspection, Ms. Wright and Ms. Navas presented you with a Form FDA 483, Inspectional Observations, and discussed the observations listed on the form with you. 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].**

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations. Section 7 of the protocol specifies procedures for collecting and reporting adverse events (AEs) and serious adverse events (SAEs). Specifically, Section 7.3.3, Nonserious Adverse Events, requires that "[a]ll identified nonserious AEs must be recorded and described on the appropriate nonserious AE page of the CRF." In addition, Section 7.3.1, Serious Adverse Events, requires that "[a]ll SAEs must be reported within 24 hours." Our investigation found several instances in which AEs and/or SAEs

identified in either clinic visits or hospital reports, were neither documented in the CRFs nor appropriately reported to the sponsor. Examples of AEs and/or SAEs which you failed to appropriately document and report include, but are not limited to, the following:

Subject#	Date	AE and/or SAE
03461	10/13/09	Shortness of Breath
12285	8/23/10	Bronchitis and Viral infection
12285	6/26/10	Neck Pain/Fall
12285	5/28/10	Fall
14055	9/15/10	Back Pain
16666	1/15/11	Fall/Head Injury
20418	12/1/10	Claudication & Edema

Failure to report adverse events jeopardizes subject safety and welfare and compromises the interpretation and validity of the investigational endpoints.

In your written response dated February 28, 2011, you state that the AEs identified were emergency room (ER) visits and that at study visits, you and the study coordinator asked subjects whether they had had any AEs or hospitalizations, and the subjects responded, "No." You further state that you believe the manner in which you interviewed these subjects and prepared charts prior to the subjects' visits needed to be improved. As a corrective action, you note that all the AEs have now been reported. To prevent the recurrence of this finding, you state that: (1) During the AE interview, information regarding ER visits, hospitalizations, and any other complaints would be requested; (2) prior to the subject's visit, chart preparation would also involve reviewing hospital records for ER visits; and (3) an in-service shall be provided to all physician's office staff to discuss communication of ER visits of research subjects.

Your response is inadequate. FDA notes that the inspection of your site in August 2008 identified findings related to delay in reporting of SAEs, and inaccuracies in documentation of AE and SAEs. In response to FDA's findings, you submitted written responses promising corrective actions. Specifically, in a December 29, 2008, written response to the FDA's August 2008 inspectional observations, you provided updated SOPs, stated that all research staff had been trained on them, and stated that they would be used for all future studies. In Attachment C, "Procedures for Managing Adverse Events," which is found in the SOP for "Adverse Event Reporting," Item #1, "Identification, assessment, and management of an adverse event," states that procedures to be utilized for ensuring that AEs are appropriately investigated include properly investigating "possible AEs documented in medical records, progress notes, etc." Your site does not appear to be following that SOP. In addition, we note that your study coordinator further informed FDA investigators that she was unaware of any active written clinical research procedures used at your site.

Given that you have not implemented the corrective actions promised in response to the August 2008 inspectional observations, we have concerns about whether the corrective actions that you have currently outlined will be properly implemented and executed in a manner that will prevent the recurrence of this and similar types of violations in the future. In your response to this letter, please provide documentation of the training your staff has received on the procedures in place at your clinical site that are intended to prevent the recurrence of this type of violation in the future. In addition, please specifically identify the mechanisms by which you will be requesting information from the subjects during the AE interview, as well as documentation of the in-service you have described regarding communication of ER visits for research subjects. Further, we request that you provide documentation to verify that the AEs and/or SAEs noted above have been reported to the sponsor. We wish to remind you that as a clinical investigator, it is your responsibility to ensure that all AE and SAEs, even those AE and/or SAEs that were ER visits, are properly collected and reported.

**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)].**

An investigator is 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.

a. According to the protocol, after reviewing a subject's international normalized ratio (INR) value, the investigator was to make the final dosing decision. You failed to maintain adequate and accurate case histories that recorded your dosing decisions for the drugs administered during the course of this investigation. Examples of this failure include, but are not limited to, the following:

The only documentation of dosing decisions for subjects was the unsigned "face sheets" filled out by the study coordinator. Our review of the face sheets for Subjects 03461, 07600, 12285, 14055, 16496, 16666, 20418, and 20544 found no documentation that you ordered the study drug dose to be maintained, withheld, or adjusted, or that you confirmed that the drug dosing decisions recorded by the study coordinator were in line with your orders.

Both you and the study coordinator stated that your site's process for relaying dosage information was as follows: The study coordinator would communicate blinded INR results to you, either verbally or via text messages, and you would tell the study coordinator to maintain, withhold, or adjust the current dose. The study coordinator would then issue dosing instructions and order drug supplies as needed, according to your verbal orders. Our investigation found that these unsigned face sheets served as the only documentation of the dosing decisions for subjects. As a result, there was no way to confirm that the drug dosing decisions recorded by the study coordinator were in line with your orders.

Failure to maintain adequate and accurate case histories compromises the interpretation and validity of the investigational endpoints.

In your written response, you stated that the INR values are called in to the study coordinator, who notifies you, and that you provide verbal orders concerning dose adjustments or your decision to suspend doses. You further stated that the sponsor provided a source document template that had the study coordinator sign off on such changes; however, you stated that you actually performed the changes. To prevent the recurrence of this finding, you stated that you would document this process via a late entry, and that you would no longer permit the use of sponsor-provided source document templates.

Your response is inadequate in that a promise that you will not use the sponsor-provided source document template does not address the cause of this violation or ensure appropriate corrective and preventive actions. As a clinical investigator, you are responsible for properly documenting the dosing and administration of drugs dispensed during the course of this clinical trial, and for ensuring that effective measures are implemented to prevent future reoccurrence.

In addition, we note that in our letter dated October 8, 2009, you had previously been cited for not preparing and maintaining adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual [21 CFR 312.62(b)]. In your undated written response (received on December 10, 2009), you stated that you would "[p]roperly document all medical decision making, including dose calculations, and ... properly complete and maintain all source documentation. All source documentation relating to medical decisions making [sic]/dose changes will be personally reviewed by me as indicated by my personal comments and signature." You have not implemented the corrective actions that you promised in your response to the October 8, 2009, letter from FDA. As a result, we have concerns about whether the corrective actions that you have currently identified in your February 28, 2011, response will be properly implemented and executed in a manner that will prevent the recurrence of these and similar types of violations in the future.

b. The requirement that an investigator maintain adequate and accurate case histories for subjects includes the requirement to ensure that informed consent forms are properly signed and dated. The records of the signed and dated informed consent forms must be adequate and accurate in the respect that they must contain all required documentation of the process through which informed consent was obtained.

In a letter dated November 1, 2010, the IRB approved a process for re-consenting of subjects who were not actively participating in the study or coming in for follow-up visits. This process required your site to mail the paper informed consent documents and to follow up with a telephone call to ensure that both the letter and the revised consent were received and understood. The IRB's November 1, 2010, letter further required that the re-consenting process be documented in the source records. Also, upon receipt of the signed copies from

the subject, the person conducting the consent discussion was to sign and date the revised consent documents to indicate that the consent discussion was conducted via telephone on the identified date. However, we note that for five subjects (Subjects 03461, 12285, 14055, 16496, and 20418), there was no documentation found in the study records regarding the telephone consent process that was used, and no documentation on the revised consent documents to indicate that the consent discussion was conducted via telephone on an identified date.

### **3. You failed to obtain IRB approval before making changes in the research [21 CFR 312.66].**

An investigator is required to obtain IRB approval before making changes in the research. The requirement for prior IRB approval includes changes in the process by which an investigator obtains informed consent of subjects.

As noted above, in a letter dated November 1, 2010, the IRB approved a process for re-consenting of subjects who were not actively participating in the study or coming in for follow-up visits. This process required your site to mail the paper informed consent documents and to follow up with a telephone call to ensure that both the letter and the revised consent were received and understood. However, you utilized this re-consenting process for five subjects (Subjects 03461, 12285, 14055, 16496, and 20418) who were still actively participating in the study and receiving study drugs. You failed to obtain IRB approval for the use of the mail and telephone re-consenting process for subjects who were still actively participating in the clinical trial.

Your written response did not provide any corrective measures to prevent the recurrence of this finding. As a result, your response is inadequate. In your response to this letter, please include corrective actions that will prevent the recurrence of this and similar types of violations in the future.

Failure to promptly obtain IRB approval for changes in the research activity, and failure to properly document the informed consent of trial subjects, can compromise the safety and welfare of subjects enrolled in the clinical investigation.

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:

Constance Cullity (formerly Lewin), 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}  
Leslie K. Ball, M.D.  
Acting Director  
Office of Scientific Investigations  
Office of Compliance

Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/

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LESLIE K BALL  
08/12/2011

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