



U.S. Department of Health & Human Services



U.S. Food and Drug Administration

[Home](#) > [Inspections, Compliance, Enforcement, and Criminal Investigations](#) > [Enforcement Actions](#) > [Warning Letters](#)

Inspections, Compliance, Enforcement, and Criminal Investigations

Lin, Henry, M.D.



Department of Health and Human Services

Public Health Service
Food and Drug Administration
Rockville, MD 20857

03/08/2010

WARNING LETTER

**CERTIFIED MAIL
RETURN RECEIPT REQUESTED**

Ref: 10-HFD-45-03-01

Henry Lin, M.D.
New Mexico Veteran's Administration Health Care System
1501 San Pedro S.E., Mail Code 1115
Albuquerque, New Mexico 87108

Dear Dr. Lin:

On September 15, 2008, Ms. Teena Aiken, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct as the sponsor-investigator of the clinical investigation (Protocol **(b)(4)**, entitled **(b)(4)** of the investigational drug **(b)(4)**). We acknowledge your assertion that prior to the September 15, 2008, inspection, **(b)(4)** M.D., had assumed the role of clinical investigator for the above-mentioned study, and that you remained only as the study sponsor. Subsequently, on July 1, 2009, Ms. Aiken met with you to review your conduct as the sponsor of the above clinical investigation.

These two inspections, September 15, 2008 and July 1 2009, are 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, the documents submitted with that report, and your July 27, 2009, letter written in response to the Form FDA 483 issued at the conclusion of the July 1, 2009, inspection, 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. Aiken presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following violations related to your responsibilities as sponsor:

1. Failure to ensure proper monitoring of the clinical investigations [21 CFR 312.50 and 312.56(a)].

According to study records, subjects were enrolled in Protocol **(b)(4)** between February 20, 2007 and September 8, 2008. Our inspection found that you did not monitor any aspect of the study. As the sponsor of Protocol **(b)(4)** conducted under Investigational New Drug Application (IND) **(b)(4)**, you were responsible for ensuring that this study was adequately monitored for compliance with regulatory requirements, thereby ensuring the data quality, and that the rights, safety, and welfare of study subjects were adequately protected. (See 21 CFR 312.56 (requiring sponsors to monitor the progress of the investigation, and to take specific steps if such monitoring reveals noncompliance with the signed investigator agreement, the investigational plan, or FDA regulations, as well as to address developing safety information.)

During the 2009 inspection, you informed the FDA investigator that the study was monitored by the Data Safety Monitoring Board (DSMB), **(b)(4)**. In addition, you informed the FDA Investigator that the DSMB was to oversee the study and issue reports every four months, or sooner if necessary, and supported this statement with an undated letter from the clinical investigator, Dr. **(b)(4)**, that was apparently faxed to you on June 29, 2009. In your written response dated July 27, 2009, you reiterated that the DSMB monitored the study, and indicated that you had obtained the DSMB reviews and the internal audit report from Dr. **(b)(4)** to provide documentation for the monitoring of the clinical study. You further explained that you thought this met your requirement for monitoring the clinical study.

We find your explanations to be insufficient. You provided no additional documentation with your response, relying only on the DSMB research monitoring plan dated February 6, 2007, and DSMB Review dated September 9, 2009, collected during the 2009 inspection, to support the assertion that the DSMB provided adequate monitoring to meet your obligations as sponsor to ensure proper monitoring of the progress of the study. Those two documents indicate only that the DSMB was to monitor adverse events, and that as of September 9, 2009, had determined that there had been no new adverse events reported since the last DSMB review. Your statements to the FDA investigator suggest that you were not aware that you were responsible for monitoring the study until you met with her during the first inspection, in 2008, after the last subjects were enrolled. While the information you provided suggests that the DSMB was intended to have an integral role in monitoring some aspects of the clinical trial, specifically, adverse events and subject safety, we remind you that your responsibility as the sponsor was to monitor the overall progress of the investigation and ensure that the investigation is conducted in accordance with the general investigational plan and protocols contained in the IND, as well as other FDA regulations.

2. You failed to obtain a signed investigator statement, Form FDA 1572, before permitting an investigator to participate in an investigation [21 CFR 312.53(c)(1)].

Specifically, you initiated a clinical investigation that was not exempt from the requirements of 21 CFR Part 312, and by your own admission, allowed Dr. **(b)(4)** to participate in the investigation as clinical investigator prior to obtaining a signed investigator statement from her.

In your written response dated July 27, 2009, you stated that no further action is needed because you provided a copy of the Form FDA 1572 to the FDA investigator during the inspection. We find your response unacceptable. The Form FDA 1572 that you provided during the inspection identified **you**, not Dr. **(b)(4)**, as the principal clinical investigator, and was signed by you on June 29, 2009, more than two years after the first subjects were enrolled. Despite supplying this documentation that indicates that you were the clinical investigator for this study, elsewhere you stated that you "took on the sponsor role for the study as the research mentor for the principal investigator, **(b)(4)**, M.D." You failed, however, to obtain a Form FDA 1572 signed by **(b)(4)**, M.D., and identifying her as the clinical investigator at any time, let alone prior to her participation in the investigation.

3. You failed to give each participating investigator an investigator brochure containing the information described in 312.23(a)(5) [21 CFR 312.55(a)].

Specifically, 21 CFR 312.23(a)(5) requires that the investigator brochure contain the following information:

- a. A brief description of the drug substance and the formulation, including the structural formula, if known.
- b. A summary of the pharmacological and toxicological effects of the drug in animals and, to the extent known, in humans.
- c. A summary of the pharmacokinetics and biological disposition of the drug in animals, and if known, in humans.
- d. A summary of information relating to safety and effectiveness in humans obtained from prior clinical studies. (Reprints of published articles of such studies may be appended when useful.)
- e. A description of possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation or with related drugs, and of precautions or special monitoring to be done as part of the investigational use of the drug.

Our inspection found that you failed to provide the clinical investigator with an investigator brochure containing the information described in 21 CFR 312.23(a)(5) before the study began. (Enrollment began on February 20, 2007.)

In your written response dated July 27, 2009, you state that no further action is needed. You attached to your written response a copy of a fax from Dr. **(b)(4)**, stating that she had submitted the investigator brochure to the Institutional Review Board (IRB) along with her IRB application on 12/6/06. We find your response inadequate. There was no investigator brochure attached to your written response, nor was it attached to the fax from Dr. **(b)(4)**, to document that the investigator brochure was given to Dr. **(b)(4)** prior to the start of the study, or to indicate whether its content satisfies the regulatory requirements.

4. You failed to review and evaluate the evidence relating to the safety and effectiveness of the drug as it is obtained from the investigator [21 CFR 312.56(c)].

Our inspection found no evidence that you reviewed or evaluated safety or effectiveness of the drug in the above referenced study, or provided such reports to FDA regarding information relevant to the safety of the drug, as required under 21 CFR 312.32.

5. You failed to submit to the FDA an annual report of the investigation [21 CFR 312.33 & 312.56(c)].

As the sponsor of Protocol , you are required to submit an annual report within 60 days of the anniversary date that the IND went into effect. Your IND went into effect on May 7, 2006; however, our inspection found no evidence that any annual reports were submitted to the FDA.

6. You failed to maintain adequate records showing the receipt, shipment, or other disposition of the investigational drug [21 CFR 312.57(a)].

As a sponsor, you are required to maintain drug disposition records to include, as appropriate, the name of the investigator to whom the drug is shipped, and the date, quantity, and batch or code mark of each such shipment. Our investigation found that you did not maintain these records.

You stated in your written response dated July 27, 2009, that it was your understanding at the time of the FDA inspection that you were to provide a letter from the **(b)(4)** Pharmacy verifying proper shipment to the FDA investigator.

You further stated that you obtained records showing receipt and shipment of the study drug. Your response, however, provided no documentation to corroborate your statements that you had obtained these documents.

7. You failed to maintain complete and accurate records showing any financial interests of investigators subject to 21 CFR Part 54 [21 CFR 312.57(b)].

In accordance with 21 CFR 312.57(b), a sponsor shall maintain complete and accurate records showing any financial interest in 21 CFR 54.4(a)(3)(i-iv) paid to clinical investigators by the sponsor of the covered study and shall also maintain complete and accurate records concerning all other financial interests of investigators subject to part 54 of this chapter. Our inspection found that for the study referenced above you did not maintain complete and accurate records showing any financial interest as described in these regulations.

8. You failed to retain records and reports for two years after shipment and delivery of the drug if discontinued and FDA has been so notified [21 CFR 312.57(c)].

Our inspection found that you did not retain any records or reports for the above referenced study. As the sponsor, you are required to retain the records and reports required by this part for two years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until two years after shipment and delivery of the drug for investigational use is discontinued, and FDA has been so notified.

In your July 27, 2009, letter in response to the Form FDA 483, you did not address this violation.

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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Branch Chief, Good Clinical Practice Branch I
Division 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,

/S/

Leslie K. Ball, M.D.
Director
Division of Scientific Investigations
Office of Compliance
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