



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

Inspections, Compliance, Enforcement, and Criminal Investigations

Mancha, Vaughn H Jr, M, D. 2/17/11



Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20906

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ref: 11-HFD-45-02-03

Vaughn H. Mancha, Jr., M.D.
339 Saint Lukes Drive
Montgomery, AL 36117

Dear Dr. Mancha:

Between September 7 and September 23, 2010, Ms. Patricia Smith, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (Protocol **(b)(4)**, entitled **(b)(4)**) of the investigational drug **(b)(4) (b)(4)**, performed for **(b)(4)**.

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 October 4, 2010, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We are aware that at the conclusion of the inspection, Ms. Smith presented and discussed with you Form FDA 483, Inspectional Observations. 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].

a. Protocol Section 9.5.3.1.5, Reporting and Documenting Serious Adverse Events, specified that "all Serious Adverse Events (SAEs) that occur beginning with the time of administration of the first dose of study medication and continuing until four weeks after administration of the final dose of study medication must be reported." The protocol further specified that each SAE was to be reported to the Contact Research Organization (CRO) by telephone or via the electronic case report form (CRF) within 24 hours of becoming aware that a subject had experienced an SAE, and that the investigator must report all SAEs and unexpected problems promptly to the IRB. Also, in Section 9.5.3.1.6, Follow-Up of Adverse Events, the protocol stated that "in the event of an unexplained, treatment-emergent, clinically significant abnormal laboratory test results [sic] or clinically significant changes in laboratory test results, the tests should be repeated immediately and followed up until the

values have returned to within the reference range or to baseline for that subject.”

(1) Subject #389204 had Week 8 laboratory tests collected on February 18, 2008, and the corresponding laboratory report that was faxed to your site on February 20, 2008, showed that the subject’s creatinine (CR) level measured 3.2 mg/dL. A progress note dated February 20, 2008, stated that subsequent to the review of the Week 8 visit laboratory report, the decision was made to terminate the subject from the study due to the elevated CR level. The progress note further stated that the subject will hold the study drug and proceed with the end of termination visit. The February 20 and 21, 2008, progress notes indicated that your site left messages for the subject to contact your office regarding the abnormal laboratory results. The subject did not contact your site until February 26, 2008, and the end of termination visit was scheduled for February 27, 2008. With respect to this SAE, we note the following:

- (a) In the time period between February 22 and February 26, 2008, when the subject called your site, you had no follow-up with the subject regarding the abnormal laboratory results. The subject’s last dose of study drug was on February 26, 2008.
- (b) You did not report the SAE of acute renal failure to the CRO until February 27, 2008. This was not within the 24-hour reporting period required by the protocol. In addition, the report to the CRO stated that the onset of the SAE and the date your staff was notified of the SAE was February 26, 2008. This is contradictory to your progress note, which stated that your site became aware of the SAE on February 20, 2008.
- (c) Your site did not report the SAE to the IRB until February 27, 2008, even though your progress note indicated that your site was aware of the SAE on February 20, 2008.

You stated that contact was made with the subject immediately by phone message, and that final verbal contact was made within 6 days. You further stated that instructions regarding study medication could not be left on phone message because it would violate HIPAA regulations. To prevent the recurrence of this finding, you indicated that when critical laboratory values are returned for a subject, the subject would be called immediately to report the values, and that the subject would be instructed on what to do regarding the investigational product. You further indicated that if the subject is not reached, you would leave messages and continue to call the subject daily, and also send a letter via **(b)(4)** to the subject’s address to notify the subject.

Your response is unacceptable. We note that your site sent a Subject Medical Review Form dated June 19, 2008, to the CRO, stating that the “Subject had labs drawn on 20 Feb 2008. They were not accessed in a timely manner. Subject went into renal failure.” Thus, your site acknowledged that this SAE was not handled properly. In addition, you provided no detail regarding corrective actions you will take to ensure that reporting of SAEs to the sponsor and to the IRB are within the protocol-specified timeframes. You also failed to describe corrective actions to ensure that the information provided to the sponsor regarding SAEs would be accurate and consistent with the source records.

(2) Subject 389062 had samples collected on October 9, 2007, and the laboratory results were faxed to your site on October 10, 2007. Records indicate that you did not document your review of the laboratory results until April 22, 2008. Your delayed review of this subject’s laboratory results is a violation of Protocol Section 9.5.3.1.6, Follow-up of Adverse Events. Specifically, since your review did not take place until over six months after you received the test results, you did not adequately determine contemporaneously whether the abnormal laboratory results reported were clinically significant and therefore were required to be repeated immediately and followed up until the values were returned to within the reference range or to the baseline for that subject. The fact that these particular samples may not have, in fact, indicated an adverse or serious adverse event is irrelevant because, if they had, they would not have been documented or followed through properly, since your review did not take place until over six months after you received the test results.

Your written response indicated that you originally signed the laboratory result page, crossed out the wrong date, and wrote “reviewed labs on 10/23/07, wrote wrong date.” This notation was then initialed and dated “4/10/07.” To prevent the recurrence of this finding, you indicated that as laboratory results are received by fax, they will be placed in a basket for the clinical investigator to review and date immediately. You further stated that the basket of faxes is checked regularly throughout the day, and the longest time between receiving the labs and reviewing them is 2 days, when labs are received during the weekend.

Your response is unacceptable. Your written response regarding the dating of the laboratory result could not be verified, because the laboratory report provided during the FDA inspection showed that for the laboratory specimens collected on October 9, 2007, there was only one signature, with a date of review of April 22, 2008. We further note that you provided no corrective actions concerning the review of laboratory reports received when you would not be available.

- b. Protocol Section 9.3.1, Inclusion Criteria, and Protocol Section 9.4.7, Prior and Concomitant Therapy, specified that subjects who had used a nonsteroidal anti-inflammatory drug (NSAID) within the 30 days

prior to study entry were ineligible for enrollment into the study. FDA's review of your source records indicated that 6 subjects (389058, 389069, 389080, 389090, 389143, and 389218) had used an NSAID within the 30 days prior to study entry but were enrolled into the study.

Furthermore, in Subject Medical Review Forms submitted by your site to the CRO, **(b)(4)**, and in a protocol deviation list submitted to the IRB, you reported that Subjects 389040 and 389111 had taken an NSAID within the 30 days prior to study entry but were enrolled into the study.

Your written response stated that as the study involved two readily available over-the-counter (OTC) medications, it was your observation that subjects often took these medications not realizing that this was a protocol violation, despite your instructing the subject otherwise. You stated that you would work better in the future by asking the subject not to take any OTC medication without notifying you prior to taking it. You indicated that as a corrective action, all subjects would be instructed to bring all concomitant medications to each visit, where they will be reviewed for exclusionary medications, and that the clinical investigator will review the inclusion/exclusion criteria at randomization and will document that the subject is qualified to be randomized.

Your response is unacceptable. FDA's review of the records found that your site was aware that several subjects had taken NSAIDs within the 30 days prior to study entry, but your site continued to enroll the subjects into the study. Your response does not address how a similar situation would be handled in the future. In addition, the worksheet you provided as your corrective action provided no information as to the procedures you would use to verify that subjects met all protocol eligibility criteria.

c. Protocol Section 9.4.7, Prior and Concomitant Therapy, and Protocol Section 9.3.2, Exclusion Criteria, Subsection 7, specified that subjects who used an acid suppressant agent within 14 days prior to study entry were ineligible for enrollment into the study. FDA's review of your source records indicated that 4 subjects (389086, 389094, 389173, and 389234) had used an acid suppressant agent within 14 days prior to study entry but were enrolled into the study.

Furthermore, in Subject Medical Review Forms submitted by your site to the CRO, in a protocol deviation list submitted to the IRB, and/or in memos to files, you reported that 4 other randomized subjects (389085, 389092, 389142, and 389247) had taken an acid suppressant agent within 14 days prior to study entry.

Your written response stated that you confirmed that Subjects 389173, 389142, 389092, 389094, and 389234 had used an acid suppressant agent within 14 days prior to study entry. For Subject 389086, you stated that the subject did not notify your site that she was taking Nexium and Zantac, and this was discovered when her medical records were received from her primary care provider. For Subject 389085, you stated that the subject was prescribed Nexium and Pepcid AC by the primary care provider after the screening visit and prior to randomization, and this was not discovered until the subject had been randomized. You indicated that the corrective action for this was to have a review of the concomitant medications at every visit, and that the investigator would review the excluded medication list with all staff.

Your response is unacceptable. Your corrective actions provided no information as to how your site will verify medical records, if obtainable and received from the primary care provider, prior to enrolling and/or randomizing subjects into the study to verify the subject's concomitant medications. In addition, you provided no corrective actions regarding procedures you will utilize to elicit from subjects all the medications they are currently taking. You also provided no corrective actions or procedures you would utilize to better instruct subjects against taking protocol-specified, excluded medications.

d. Protocol Section 9.5.3.4, Clinical Laboratory Tests, specified that at the screening visit, blood samples were to be collected from study subjects for on-site testing for serum H. pylori. Protocol Section 9.3.2, Exclusion Criteria, Subsection 6, further specified that subjects with a documented current H. pylori infection were ineligible for enrollment into the study. Source records indicated that at least 2 subjects (389127 and 389135) were enrolled into the study without documentation of a current negative H. pylori test at the screening visit.

Furthermore, in Subject Medical Review Forms submitted by your site to the CRO, in a protocol deviation list submitted to the IRB, and/or in memos to files, you reported that additional subjects, including but not limited to Subjects 389129, 389137, and 389142, were enrolled into the study without documentation of a current negative H. pylori test performed at the screening visit.

Your written response stated that this protocol violation was an isolated issue and that the clinical research coordinator (CRC) who inadvertently did not document the results was "re-educated." You also indicated that, as a corrective action, any in-house test to be performed will have the lot number, expiration date, and results documented in the source documents.

Your response is unacceptable. Specifically, your statement that the CRC inadvertently did not document the result implies that the CRC actually performed the testing, but did not record the results in the source records.

According to the establishment inspection report, you informed FDA Investigator Smith that while observing this particular CRC's work, you noticed that she was not using any of the supplies needed for the H. pylori test but was writing on the source records that she had in fact conducted those tests. Documentation found at your site also stated that the CRC in question either did not conduct any H. pylori testing at the screening visit, or that the testing was questionable because the supplies needed for the test were not used. You further informed FDA Investigator Smith that when you questioned the study coordinator about your discovery and suggested that she would have to undergo training and work under the supervision of other coordinators, she abruptly resigned. Therefore, FDA cannot confirm that the CRC in question was "re-educated," as you stated in your written response.

e. In addition to the above protocol violations, in written memos to file, Subject Medical Review Forms submitted to the CRO, and/or protocol deviations sent to the IRB, your site acknowledged numerous protocol deviations, including but not limited to lack of international normalized ratio (INR) testing at the screening visit for subjects on anticoagulant therapy (e.g., 389017 and 389085); dispensing incorrect test articles to subjects (e.g., 389013, 389041, and 389091); study visits not being scheduled according to the protocol (e.g., 389162 and 389040); and failure to conduct screening serum pregnancy tests (e.g., Subjects 389075 and 389211).

In your written response, you confirmed the findings noted above. Your corrective actions included (1) a commitment to reduce human error by having a better understanding of each protocol and all of its procedures, and by total adherence to the protocol; (2) creation of a source document appendix to allow a second coordinator to cross-reference the investigational product (IP) or kit number assigned by the interactive voice recognition system (IVRS) for a particular subject, so that two coordinators can verify that the correct IP is dispensed to the subject; (3) development of a worksheet entitled "Visit Schedule" that includes the projected dates and actual dates of each visit including +/- windows; and (4) development of a new source document to be used at the end of every visit, certifying that the investigator has reviewed the source documents in their entirety for accuracy and correct documentation.

While these corrective actions appear appropriate, it was the absence of such measures during the conduct of these trials that led to the violations listed here, and that increases our concerns over your approach to ensuring appropriate human subject protection.

2. You failed to 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)].

a. The screening visit source record for Subject 389137 had a signature which appeared to be that of sub-investigator, Dr. (b)(4), documenting that he had performed a physical exam on October 11, 2007. Your records indicated, however, that Dr. (b)(4) confirmed that the signature on the screening visit source record was not his and denied performing the examination.

You provided no written response to address this finding.

b. Source records indicated that Subject 389230 had a physical exam at the screening visit on December 18, 2007. However, you did not sign the source physical exam record until April 21, 2008.

Your written response indicated that the physical exam was done at the screening visit, but that you inadvertently forgot to fill out the source document. Your corrective action to prevent this finding was to have the investigator thoroughly document, sign, and date all of the physical exams in real time.

Your response is inadequate. You provided no information regarding procedures and/or training that you would require to ensure that documents are completed, signed, and dated at the time of the study visit.

c. Records at your site are discrepant concerning which subject (i.e., 389198 or 389168) had the Week 24 visit out of window. Specifically, your site reported in the Subject Medical Review Form dated May 20, 2008, that Subject 389168 (randomization number 5168) had the Week 24 visit scheduled 3 weeks early. In the upper right-hand corner of this same form, there is a handwritten note stating "#389198." According to the enrollment log, Subject 389168's randomization number was not 5168; this randomization number belonged to Subject 389198. In the (b)(4) IVRS Deactivation worksheet, you again stated that Subject 389168's Week 24 visit was out of window.

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.
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Sincerely yours,

{See appended electronic signature page}

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

LESLIE K BALL
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