

Inspections, Compliance, Enforcement, and Criminal Investigations

Hijazi, Saad, M.D. 5/19/09

[hhsbluebird](#)Department of Health and Human Services

Public Health Service
Food and Drug
Administration
Rockville, MD 20857

MAY 19 2009

WARNING LETTER

CERTIFIED MAIL

RETURN RECEIPT REQUESTED

Ref.#: 09-HFD-45-05-01

Saad Hijazi, M.D.
1151 Hospital Way
Building D, Suite 100
Pocatello, ID 83201-5091

Dear Dr. Hijazi:

Between October 27 and December 2, 2008, Mr. Thomas Gordon, representing the Food and Drug Administration (FDA), conducted an investigation to review your conduct of a clinical investigation (Protocol **(b)(4)** entitled **(b)(4)** performed for **(b)(4)**

This inspection is a 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 and the documents submitted

with that report, 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, Mr. Gordon provided and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You failed to maintain 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 FDA’s review of the source documents for the records audited during the inspection, there were numerous instances where either (a) information entered into the case report forms (CRFs) did not match the information in the source documents or (b) information in the source documents was changed after the subject had completed the study, up to two years post-completion, and it could not be determined where the information related to the change was derived. Examples include but were not limited to the following:

A. For Subject #0001:

Date of visit	Type of contact with subject	Clinical symptom	AECB related signs and symptoms assessment log	CRF
January 25, 2006	Telephone Contact	Dyspnea	Worse	Same
		Sputum Production	Same	Worse
		Sputum Purulence	Mostly clear ¹	yellow, green, cloudy and thick
January 26, 2006	Telephone contact	Cough	Worse ²	Worse
		Dyspnea	Worse ²	Same
		Sputum Production	Same	Worse
February 13, 2006	Clinic visit	Cough	Absent	Mild
		Wheezing	Mild ¹	Mild
		Rales	Mild ¹	Mild

1 Log entry changed on March 15, 2006

2 No date to show when the information was changed on the Log

For those items noted with the footnotes ¹ or ² above, we note that the information in the source record was changed after the subject had already completed the study (study completion February 13, 2006). FDA’s review of the source records for this subject could not determine where your site obtained the information to corroborate the noted changes your site made to the original source record (i.e. the AECB related

signs and symptoms assessment log).

B. For Subject #0002:

Date of visit	Type of contact with subject	Clinical symptom	AECB related signs and symptoms assessment log	CRF
January 29, 2006	Telephone	Cough	Improved ¹	Improved
		Dyspnea	Improved ¹	Improved
		Sputum Production	Improved ¹	Improved
January 31, 2006	Clinic visit	Sputum Production	Mild ¹	Mild
		Sputum Purulence	Yellow, green, cloudy and thick	Nothing Listed
		Wheezing	Mild ¹	Mild
		Rales	Mild ¹	Mild
		Ronchi	Absent ¹	Absent
		Decreased Breath Sounds	Absent ¹	Absent

1 Log entry changed on March 16, 2006

For those items noted with the footnote ¹, the information in the source record was changed after the subject had already completed the study (study completion February 14, 2006). FDA's review of the source records for this subject could not determine where your site obtained the information to corroborate the noted changes your site made to the original source record (i.e. the AECB related signs and symptoms assessment log).

C. For Subject #0003:

Date of visit	Type of contact with subject	Clinical symptom	AECB related signs and symptoms assessment log	CRF
February 6, 2006	Telephone	Cough	Nothing listed	Improved
		Dyspnea	Nothing listed	Improved
		Sputum Production	Nothing listed	Improved
		Sputum Purulence	Nothing listed	Mostly Clear

Per the protocol deviation form sent to the IRB, you noted that for the telephone contact your site made to Subject #0003 on February 6, 2006, you did not capture the AECB signs and symptoms of disease. As your site did not capture the AECB signs and symptoms of disease, it could not be determined how you could have reported information to the CRF.

D. For Subject #0004:

Date of visit	Type of contact with subject	Clinical symptom	AECB related signs and symptoms assessment log	CRF
February 10, 2006	Telephone	Sputum Purulence	Mostly Clear ¹	Mostly Clear
February 11, 2006	Telephone	Cough	Improved ²	Improved
		Dyspnea	Improved ²	Improved
		Sputum Production	Improved ²	Improved
		Sputum Purulence	Mostly Clear ¹	Mostly clear

1 Log entry changed on June 24, 2008

2 Log entry changed in November 2006

For those items noted with the footnotes ¹ or ² above, we note that the information in the source record was changed after the subject had already completed the study (study completion March 7, 2006). With respect to the changes made on June 24, 2008, records indicate the changes were made by study coordinator **(b)(6)**, who per the report to the Center, was not a part of the original study. In addition, FDA's review of the source records for this subject could not determine where your site obtained the information to corroborate the noted changes your site made to the original source record (i.e. the AECB related signs and symptoms assessment log).

E. For Subject #0010, for the baseline office clinic visit on April 13, 2006:

Pre-Exacerbation signs and symptoms	(b)(4) Source Document	CRF
Cough	Absent*	Mild
Sputum Production	Absent*	Mild
Sputum Purulence	Absent*	Moderate (aka mucopurulent)

For those items noted with an * above, the changes to the source document were made on June 24, 2008, two years after the completion of the study, by study coordinator **(b)(6)**, who per the report to the Center, was not a part of the original study.

F. For Subject #0012 for the Test of Cure Visit on June 27, 2006:

Clinical symptom	AECB related signs and symptoms assessment log	CRF
Sputum Purulence	Mucoid*	Absent

For the item noted with an * above, the change to the source document was made on

July 2, 2008, two years after the completion of the study, by study coordinator **(b)(6)**, who per the report to the Center, was not a part of the original study. FDA's review of the source records for this subject could not determine where your site obtained the information to corroborate the noted changes your site made to the original source record (i.e. the AECB related signs and symptoms assessment log).

G. For Subject #0015, for the during study clinic visit on July 14, 2006:

Clinical symptom	AECB related signs and symptoms assessment log	CRF
Cough	Same	Severe
Dyspnea	Improved	Moderate
Sputum Production	Improved	Moderate
	Cloudy/thick	
Sputum Purulence	Mucoid not circled as a response.	Mucoid

It is unclear how or why changes to source documents were made at your site following subject completion from the study. Given the numerous inaccuracies noted in the source documents and CRFs audited at your site, FDA is unable verify the integrity of data collected at your site.

2. You failed to obtain the informed consent of each human subject in accordance with 21 CFR part 50 [21 CFR 312.60].

Under 21 CFR 312.60, an investigator is required to obtain the informed consent of each human subject in accordance with 21 CFR part 50. FDA's regulations at 21 CFR 50.20 state that except as provided in 21 CFR 50.23 and 21 CFR 50.24, no investigator may involve a human being as a subject in research covered by the regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. The regulation specifies that an investigator shall seek such consent only under circumstances that provide the prospective subject or the subject's representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. Section 50.27 of FDA's regulations further provide that informed consent shall be documented by the use of a written consent document approved by the IRB, which is to be signed by the subject or subject's representative only after the subject or the subject's representative is given adequate opportunity to read the document.

Subject #0004 signed the original informed consent form to be enrolled into the study on February 7, 2006. In a letter dated March 1, 2006, the IRB informed your site that they had approved informed consent form version 021706 which included modifications that were made to the risks section. The IRB's letter further stated that current and new subjects were to sign the revised informed consent form. There was no documentation found during the FDA inspection to show that your site re-consented Subject #0004, who was still enrolled into the study at the time, with

the revised informed consent form to inform them of the possible additional risks the subject may experience.

3. You failed to conduct the studies or ensure they were conducted according to the investigational plan [21 CFR 312.60].

A. Protocol Amendment #2 and #3 stated that subjects receiving concomitant therapy with medications including but not limited to HMG-CoA reductase inhibitors (e.g. simvastatin, lovastatin, or atorvastatin) were to be excluded from the study. In addition, both protocols noted that during the study, concomitant administration of HMG-CoA reductase inhibitors with telithromycin should be avoided. For five of ten subject records reviewed (Subject #0001, #0005, #0010, #0015, and #0017), source records indicate that these subjects were enrolled into the study even though they were either receiving concomitant therapy with HMG-CoA reductase inhibitors prior to enrollment into the study or began their use after your site had enrolled them into the study.

With respect to Subject #0001, a source document noted that your study coordinator contacted via telephone, the study sponsor, on February 7, 2006 requesting information as to whether this subject who had started study medication but did not discontinue the use of a HMG-COA inhibitor until Day 2 should be withdrawn from the study. In an email dated February 7, 2006, the sponsor noted that subsequent to the question posed by your study coordinator, this subject should not be discontinued from the study. In review of the records, however, FDA notes that by the time the question was posed by your study coordinator to the sponsor, Subject #0001 had completed taking all study drug (January 28, 2006), completed the test of cure visit (February 2, 2006) and only had the follow up visit remaining. In addition, records indicate that the HMG-COA inhibitor was not withdrawn on Day 2 of the study as was reported to the sponsor.

B. Protocol Amendment #3 stated that to be included into the study, the subject was to have evidence of airflow obstruction (within the year prior to the current exacerbation or during the current exacerbation and then reconfirmed after recovery), defined as:

- Forced expiratory volume in one second (FEV_1) % predicted > 35 and
- Ratio of FEV_1 to forced vital capacity (FVC) < 0.70

Source records indicate that Subject #0017 had an FEV_1 /FVC ratio of 0.72 and thus did not meet this inclusion criterion and further was also not granted a waiver by the sponsor for enrollment into the study, but your site continued to randomize the subject into the study.

C. Protocol Amendment #3 stated that the study drug was to be stored in a limited access area or in a locked cabinet under appropriate environmental conditions at or below 25°C (77°F). Our inspection found that there were no records after the date of April 6, 2006 to confirm that the study medication was stored appropriately per the protocol requirements. Therefore, FDA is unable to confirm the integrity of the investigational product that was dispensed to the subjects following April 6, 2006.

D. Subject #0021 was consented and enrolled into the study during a time when the study was placed on "hold" by the sponsor. In a fax dated December 22, 2006 to your site, (b)(4) informed you that due to an FDA advisory committee meeting that discussed the use of telithromycin, (b)(4) and (b)(4) made the decision to remove telithromycin as the active comparator drug from the protocol. The letter specifically stated "What this means most immediately to you is that enrollment in the current protocol will be temporarily stopped as of the writing of this letter. This is not a regulatory "hold" in that no regulatory agency has requested this action. The Interactive Voice Response System (IVRS) will be temporarily "shut off" and you will be unable to randomize any further subjects. Any subjects currently active in the study should complete all scheduled visits". Documentation found at your site showed that this hold on enrollment was not removed by (b)(4) until February 27, 2007.

Source documents show that your site enrolled Subject #0021 into the study on January 5, 2007 during the time of the sponsor's hold and further that your site performed study related procedures including but not limited to taking vitals, performing a medical history, spirometry test and chest x-ray, collecting sputum and laboratory samples, and reviewing the subject's eligibility into the study. Per the progress note found during the inspection, it was only after someone at your site contacted the IVRS to try to randomize this subject were you were unable to do so as (b)(4) had temporarily stopped randomization of subjects into the study using the IVRS. As records obtained at your site showed that your site had been informed on December 22, 2006, prior to this subject's enrollment, that the sponsor had temporarily stopped enrollment of subjects into the protocol, your site should not have enrolled Subject #0021 into the study.

4. You failed to assure that an Institutional Review Board (IRB) complying with applicable regulatory requirements was responsible for the continuing review and approval of a clinical study [21 CFR 312.66].

Per the original IRB approval letter sent to your site, the IRB had informed your site that the study expired on January 3, 2007. We note that your site was informed of the IRB's approval of the continuing review of the study in a letter dated January 31, 2007. Thus, between January 3, 2007 and January 31, 2007, your site had not been informed that the study was re-approved for continuing review and thus during this time your site should not have enrolled any new subjects into the study. As noted above, your site enrolled Subject #0021 into the study on January 5, 2007.

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 on-going 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 or will be taking 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 Tejashri Purohit-Sheth, M.D., at

301-796-3402; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Tejashri Purohit-Sheth, M.D.
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Good Clinical Practice Branch II
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10903 New Hampshire Avenue
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Sincerely yours,

/S/

Leslie K. Ball, M.D.
Director
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research