DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ashok Shah, M.D.
3808 South Hopkins Avenue
Titusville, FL 32780

Ref: 08-HFD-45-0111

Dear Dr. Shah:

Between April 30, 2007 and May 17, 2007, Ms. Brunilda Torres, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of the following clinical investigations of the investigational drug Telithromycin (Ketek®), performed for Sanofi-Aventis Pharmaceuticals (formerly Aventis Pharmaceuticals):

1. Protocol[ ]"A Randomized, Double-Blind, Parallel-Group, Multicenter, Study to Compare Clinical Health Outcomes of Telithromycin versus Azithromycin in Outpatients with Community-Acquired Lower Respiratory Tract Infections."

2. Protocol[ ]"A Randomized, Open-Label, Multicenter Trial of the Safety and Effectiveness of Oral Telithromycin (Ketek®) and Amoxicillin/Clavulanic Acid (Augmentin®) in Outpatients with Respiratory Tract Infections in Usual Care Settings."

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.

Based on this inspection, and from our review of the establishment inspection report and its supporting documents, 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. At the conclusion of the inspection, Ms. Torres presented and discussed with you the Form FDA 483, Inspectional Observations. We acknowledge receipt of your letter dated May 18, 2007, responding to some items on the Form FDA 483, and wish to emphasize the following:

1. **You failed to conduct the study in accordance with the investigational plan [21 CFR 312.60].**

Protocol

a. Nine (9) out of 13 enrolled subjects failed to meet eligibility criteria with respect to pulmonary function testing. For enrollment, Protocol Section 4.2.1 required that subjects have a documented history of chronic bronchitis with 1) a basal FEV_1 between 70% and 35% predicted and 2) an FEV_1 /FVC <70% in the past 12 months. You failed to ensure that all enrolled subjects met Pulmonary Function Test (PFT) inclusion criteria, which was integral to the diagnosis of AECB.

   i. For Subjects 1 and 5, PFT results used to enroll subjects lack the subjects' demographic information, and the date that the test was performed. FEV_1 and FEV_1 /FVC eligibility criteria could not be verified as the pulmonary function test on file did not contain the header which includes subject information and demographic data (name, date and time of test, gender, medications, height, weight, etc.), which is printed on the top of the page. It appears that this top section was removed, making it difficult to confirm the subject's identity and therefore subject eligibility for entry. You were unable to provide additional documentation to verify the source of these PFT reports.

   ii. For Subjects 2, 4, 8, and 11, there was no qualifying PFT on file at the time of the inspection.

   iii. For Subjects 3, 7, and 12, PFT reports reveal that these subjects failed to meet inclusion criteria as their FEV_1 and/or FEV_1 /FVC measurements were not < 70%.

   In your May 18, 2007 written response, you stated that the PFT requirement was misunderstood by you. This is not an acceptable response. As a principal clinical investigator, you are required to understand and adhere to the requirements set forth in the protocol. Your failure to adhere to inclusion criteria as specified in the protocol has not only raised questions about the validity of the data generated by your site, but also exposed subjects, who may not have been eligible for study entry, to unnecessary risk.

b. For enrollment, Protocol Section 4.2.1 required that subjects have a documented history of chronic bronchitis with at least one episode of an acute exacerbation of chronic bronchitis (AECB) in the past 12 months. You failed to ensure that all subjects met this protocol specified criterion. For example,

   i. There is no source documentation to support that Subject #1 had at least one episode of AECB in the past 12 months. Although there is a handwritten note on the bottom of the dictated note dated 1/13/06 stating that the subject had 2 episodes of AECB, the last reported one in June 2005, there are no supporting

documents in the subject's medical records to confirm these statements.

ii. There is no source documentation to support that Subject #2 had at least one episode of AECB in the past 12 months. The dictated clinic visit note dated 11/21/05, which is listed as the qualifying visit for documentation of AECB in the past 12 months in the CRF, states under "Assessment," that the subject had "Acute simple bronchitis." However, there is a handwritten annotation which lists AECB, which is not dated, and there is no explanation for the annotation. As acute simple bronchitis is quite different from acute exacerbation of chronic bronchitis (AECB), it is difficult to support that this subject had an AECB within the past 12 months per this documentation.

c. Protocol Section 7.2.1 required that women of childbearing potential have pregnancy tests conducted. You failed to administer pregnancy tests in Subjects #4 and #11.

We acknowledge your May 18, 2007 response, in which you stated that Subject #4 was menstruating at the time of enrollment; however, we find your response unacceptable. The protocol did not provide any exceptions with respect to conducting a pregnancy test and concurrent menstruation.

With respect to Subject #11, we acknowledge your response that this subject had early menopause. However, there is no source documentation to support that this subject had early menopause. Furthermore, note that on page 6 of the Source Document Worksheet for Visit 1, it lists "natural menopause with dysfunctional uterine bleeding," however, this has been crossed out without explanation. It is unclear why this was crossed out.

d. Protocol Section 4.3 lists known renal dysfunction as an exclusion criterion. However, you enrolled Subject #8 into this study, when this subject has chronic renal insufficiency, per documentation by a clinic note visit to the [ ] Medical Office, dated 7/27/04.

This subject should have been excluded from study entry. Your failure to exclude this subject from the study exposed the subject to potential harm, given his concomitant renal insufficiency.

e. Protocol section 6.2.1 prohibits the concomitant use of simvastatin, lovastatin, or atorvastatin with telithromycin. However, Subjects #1 and 12 were prescribed medications that were prohibited under the protocol exclusion criteria. For example,

i. For Subject #1, the Study Summary Forms for Previous and Concomitant Treatments (page 30 of the CRF) lists Vytorin (a combination of ezetemibe and simvastatin) as ongoing therapy initiated on 06 JUN 2005. There is no end date provided and the tick box for "ongoing? (at end of therapy)" is checked off.

ii. For Subject # 12, the dictated note corresponding to the baseline visit, 2/22/06, lists Advicor (a combination of Niacin and lovastatin) as an ongoing medication. However, there is no evidence in the subject's records that Advicor was discontinued.

We acknowledge your May 18, 2007 response letter that states that it is your practice to stop all statin drugs in patients on antibiotic therapy for 5-7 days and "therefore, this patient didn't take any statins during the trial." However, source and CRF documentation do not support this statement.

f. Protocol Section 5.5 required that study drugs be locked in an area with restricted access; however, per your own admission to the FDA investigator, the study drug was kept inside an unlocked cabinet used to store medical samples and the cabinet was inside an unrestricted access room where the clinic photocopy machine was kept.

Protocol [redacted]

g. Protocol section 6.2 required that "all treatments being taken by the subjects on entry to the study or at any time during the study…be documented as such on the case report form." Concomitant medications or antibiotics taken within the last seven days were not reported on the case report form for the following subjects:

i. Subject #17 received a Cefazolin injection
ii. Subject #19 received a Lincocin injection
iii. Subject #33 received a Cefazolin injection
iv. Subject #59 received a Cefazolin injection

The use of concomitant antibiotic treatments in a study evaluating the efficacy of an antibiotic can critically affect the interpretation of results of the study, and therefore the failure to report such concomitant therapies could potentially impact study outcome.

h. Protocol Section 8.3 requires that all adverse events that occur during the observation period set forth in Section 8.2 must be documented on the pages provided in the case report form. For Subject #68, you failed to report two separate adverse events on the case report form. Specifically,

i. Subject #68 reported that she experienced left hand tingling for four days at Visit #2.

ii. Subject #68 reported "lightheadedness and blurry vision when sugar drops" as documented on your clinic visit form dated 2/27/03 and you documented "dizzinesss and passing out spells" on your dictated note for Visit #3. However, this was not reported on the CRF. Furthermore, Protocol Section 8.1.4 required that blurred vision be reported as an adverse event of special interest; however, you failed to report this on the case report form.

i. Protocol Section 7.2.2 required that post-therapy visits be completed within 17 to 22 days of the initial Visit 1. For Subjects #31, #61, and #68, Visit 2 was not conducted within the required protocol window.

2. 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)].

Protocol [ ]

a. In several instances, the study-visit dictated notes were modified by retroactive handwritten annotations on the record, which were not dated. Per your own admission at the time of the inspection, the dictated notes were not available for an average of four days post-dictation. These annotations included, but were not limited to AECB symptoms and peak flow results. Since these handwritten annotations were not dated, the date that the information was added could not be verified. Examples include, but are not limited to the following:

i. For Subject #5, the dictated note dated 9/29/05 includes a handwritten annotation of "AECB" which is not dated. However, the assessment stated upper respiratory tract infection. There is no explanation as to why AECB was annotated on this note nor when this annotation was made.

ii. For Subject #2, the bottom of the dictated note dated 1/16/06 documents peak flow values of 140, 130, and 120; however, there is no source documentation to support the addition of these measurements 4 days later.

iii. For Subject #3, the bottom of the dictated note dated 1/17/06 documents peak flow values of 100, 110, and 100; however, there is no source documentation to support the addition of these measurements 4 days later.

b. For 12 of 13 subjects, you made retroactive corrections to data on the clinic visit form, CRF and /or Source Document Worksheets without explanation. Examples include but are not limited to the following:

i. For Subjects #1, #2, #4, and #5, on the CRF for Visit 1, lung function test entries are listed; however, they are later crossed out without rationale.

ii. For Subject # 1, it is noted that on the CRF for the baseline visit, you had initially noted that the subject met all inclusion and exclusion criteria; however, on 7/25/06 (over 5 months after subject enrolled into the study) the record was annotated to state that the subject did not meet all eligibility criteria.

iii. For Subject #4, a temperature of 97.9 was crossed out and 99 was written on the clinic visit form for Visit 1, dated 1/23/06. There is no written explanation

as to why the temperature was changed.

iv. Additionally for Subject #4, there are several entries crossed out on the Visit 1 Relevant Medical/Surgical History section on the CRF, to include "Diabetes," and "not sexually active and menstruating," without explanation.

v. For Subject #8, on the CRF for Visit 1 dated 2/8/06, "Diabetes Mellitus," is crossed out without explanation.

vi. For Subject #11, on the bottom of the dictated clinic note dated 2/17/06, there is a handwritten annotation that states "allergy to Ketek," which has later been crossed out. Note that the subject was entered into the study on 2/17/06 and the date of the correction is 4/27. No explanation was provided for the correction.

c. Discrepancies were noted between information on your dictated clinic notes, clinic visit forms, source document worksheets and/or CRFs for various subjects. Examples include but are not limited to the following:

i. For Subject # 12, the qualifying episode of AECB was listed as 05 March 2005 on the CRF; however, per the dictated clinic note, the date of the visit was 3/25/05.

ii. For Subject #5, the dictated clinic note dated 1/26/06 documents that the subject had rales and wheezes; however, the Source document Worksheet for 1/26/06 documents rales and wheeze as absent.

iii. For Subject #4, on the Source Document Worksheet for Visit 1, the box in response to whether the female is of childbearing age is checked "No." However, on the CRF for Visit 1, this box is checked as "yes" and circled as a correction.

iv. For Subject #8, the Source Document Worksheet for Visit 1 dated 2/8/06, documents that the subject had mild sputum production; however, the dictated clinic visit note or the clinic visit form for this same date fails to provide source documentation for the sputum production.

3. **You failed to obtain informed consent prior to involving a human being as a subject in clinical research. [21 CFR 50.20]**

Protocol [redacted]

Specifically, Subject #1 signed the Informed Consent Document on 11/15/01; however, the CRF documents that the subject was entered into the study on 11/5/01. Per this documentation, the subject was enrolled into the study prior to obtaining informed consent.

4. **You failed to properly document written informed consent in that the Informed Consent Document was not signed or dated by the subject or the subject's legally authorized representative. [21 CFR 50.27(a)]**

   Protocol [redacted]

   Specifically,

   a. For Subject #1, it appears that the subject did not sign the Informed Consent Document. The signature in the signature block of the informed consent appears quite distinct from that noted on the signature on the Authorization to Use and Disclose Personal Health Information.

   b. None of the subjects dated the Informed Consent Document per your own admission at the time of the inspection, when you stated that you dated the Informed Consent Documents of all participating subjects.

5. **You failed to provide a copy of the signed and dated written Informed Consent Document, which had been approved by the IRB to the subject or subject's legally authorized representative [21 CFR 50.27(a)].**

   Protocol [redacted]

   a. There is no documentation available to indicate that a copy of the signed and dated Informed Consent Document was provided to each subject. This was confirmed by your own admission to the FDA Field Investigator at the time of the inspection that you did not provide the subjects a copy of the signed Informed Consent Document.

   Protocol [redacted]

   b. For Subject #19, study visit notes dated 12/17/2001 indicate a copy of the Informed Consent Document was provided to the subject on 12/15/2001, two days before the subject was actually consented. There is no documentation to indicate that this subject attended the clinic on 12/15/2001.

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 must 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 must 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 Joseph Salewski, at (240) 276-8821; FAX (240) 276-8844. Your written response and any pertinent documentation should be addressed to:

Joseph Salewski
Deputy Director
Division of Scientific Investigations/HFD-45
Office of Compliance
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

Sincerely yours,

{See appended electronic signature page}

Leslie Ball, M.D.
Director
Division of Scientific Investigations/HFD-45
Office of Compliance
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Leslie Ball
3/19/2008 05:09:28 PM