N47L

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NOTICE OF INITIATION OF DISQUALIFICATION PROCEEDINGS AND OPPORTUNITY TO EXPLAIN (NIDPOE)

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Manjeet Kaur Achreja, M.D.
Seagrove Medical Clinic
614 N. Broad Street
Seagrove, North Carolina 27341

Dear Dr. Kaur Achreja:

Between August 25 and September 3, 2003, Ms. Eileen J. Bannerman and Ms. Tracy R. Ball representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of the following clinical study:

> Protocol [ ] entitled "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 study of the investigational drug telithromycin was performed for Aventis Pharmaceuticals, Inc.

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 the study have been protected.

Based on our evaluation of information obtained by the Agency, we believe that you have submitted false information to the FDA or sponsor in required reports and repeatedly or deliberately violated regulations governing the proper conduct of clinical studies involving investigational products as published under Title 21, Code of Federal Regulations (CFR), Part 312.

This letter provides you with written notice of the matters under complaint and initiates an administrative proceeding, described below, to determine whether you should be disqualified from receiving investigational products as set forth under 21 CFR 312.

A listing of the violations follows. The applicable provisions of the CFR are cited for each violation.

1. **You submitted false information to the FDA or sponsor in a required report [21 CFR 312.70].**

During our inspection, we audited the records of 37 out of a total of 116 subjects enrolled at your site. We found that progress notes (medical records) for subjects [redacted] and [redacted] were backdated. Progress notes for subject [redacted] dated 12/5/01, for subject [redacted] dated 12/23/01, and for subject [redacted] dated 1/17/02 were all completed on a form with the following information: "© 2003 [ ] and "Printed in USA/April 2003." We note that this form was copyrighted and printed in 2003 and would not be available until well after the dates of the progress notes, ostensibly written in 2001 and 2002.

In addition, the Case Report Form (CRF) for subject [redacted] recorded "Headache" as an adverse event (AE) with a start date of 2/26/02 and end date of 2/27/02. However, the progress notes covering the period between 1/18/02 - 2/29/02 indicate that Headache occurred on 2/29/02 (February only had 28 days in 2002). During the inspection, you produced an additional progress note concerning this AE, which was backdated. This progress note, dated 2/26/02, indicates the onset of Headache as 2/26/02, but was written on a form that was not available until 2003 (same form as above stating "© 2003 [ ] and "Printed in USA/April 2003").

Protocol [ ] (Protocol [ ] Section 12.9 "Record Retention," requires that study subject medical records be maintained, specifying that "[e]ssential documents should be retained until at least 2 years after the first approval of a marking application...Essential documents include...[a]ll other source documents (subject medical records, hospital records, laboratory records, etc.," and "[a]ll other documents as listed in section 8 of the ICH E6 Guideline for Good Clinical Practice (Essential Documents for the Conduct of a Clinical Trial)." ICH E6, item 8.3.13 requires retention of source documents "to document the existence of the subject and substantiate integrity of trial data collected' and "to include original documents related to the trial, to medical treatment and history of the subject."

In addition, Protocol [ ] explicitly requires that the sponsor must have access to these source documents to verify data. Section 13 of Protocol [ ] "Study Monitoring and Audit" states that "[m]onitoring and auditing procedures developed or endorsed by the sponsor will be followed, in order to comply with GCP guidelines. Direct access to the on-site study documentation and medical records must be ensured." Further, Section 13.1 of Protocol [ ] "Study Monitoring and Source Data Verification" states "[m]onitoring will be done according to the monitoring plan by representative of the sponsor (study monitor) who will check the case report forms for completeness and clarity, and crosscheck them with source documents..." Finally, Section 13.2 "On-Site Audits" states: "[d]omestic and foreign regulatory authorities, the IEC.IRB, and an auditor authorized by the sponsor may request access to all source documents, case report forms, and other study documentation for on-site audit or inspection."

Thus, the medical records were required to be maintained by the protocol and by 21 CFR 312.62, and be available for review by the sponsor, the sponsor's designated monitor or auditor, and FDA. In addition, these source documents served as the basis for the data recorded in the CRFs that were submitted to the sponsor, and ultimately to FDA in a New Drug Application.

In your October 7, 2003, written response to FDA you stated that you discovered in April 2003 during an annual review that certain subject files were missing. You stated "[f]or documentation's sake, to complete the record, I re-wrote the notes for those days, with the help of CRFs' and AE [adverse event] forms. As these patients were my active patients, I was able to rewrite most of the things accurately. I made the error that, I did not acknowledge that these notes were re-written and should have signed and dated them according to the dates that I had written them again." We find your explanation for backdating of documents to be unacceptable. The backdating of documents raises significant questions regarding the credibility of your study records, and thus the reliability of the data submitted to the sponsor and FDA.

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)].**

In addition to the items identified in #1 above, our investigation identified a range of violations concerning the adequacy and accuracy of subject records [CRFs and source documentation] for this study. Specifically, our investigation found inconsistencies between CRFs and source records, inconsistencies within CRFs, and inconsistencies within source records. For example:

a. The CRF for subject [redacted] for study visit 3 is dated January 12 (and the year was left blank). The source documentation for study visit 3 is dated 1/28/02. In your written response, you stated that the date on the CRF was wrong and that study visit 3 occurred on 1/28/02.

b. For study visit 3 for subject [redacted] there are three different progress notes dated 2/7/02, 2/22/02, and 3/1/02. In your written response, you indicated that the 2/7/02 progress note was erroneously characterized as the visit 3 progress note. You stated that study visit 3 occurred on 3/1/02. According to the protocol, study visit 3 should have occurred between 2/21/02 and 2/26/02. It is unclear from your documentation on what date study visit 3 occurred, and which is the correct progress note.

c. For subject [redacted] there are two different progress notes for the study visit on 12/21/01. One note records an apparent AE ("made her feel bad, nervous, shaky") and states that the subject "did not finish med." The other note states that the subject had "no complaints, no side effects" and seems to indicate that she completed the course of study medication ("she completed as directed"). In your written response, you stated that there were two notes for this visit because the subject was seen by both the physician's assistant and the physician and there was a difference of opinion about whether to report nervousness (chronic problem) as

an AE. However, your response failed to address the inconsistent statements regarding whether the subject completed the study medication.

d. For subject [redacted] there are two different versions of Page 1 of the CRF for study visit 1. These CRFs contain conflicting information concerning the subject's medical history, the need for dose reduction due to renal impairment, and the subject's date of birth. In your written response, you stated that the nurse wrote the wrong information on one CRF so she completed another CRF. However, the CRFs do not indicate which is the corrected form and which is in error.

e. The CRF indicates that subject [redacted] withdrew from study at study visit 2 on January 11, 2002 because the subject did not wish to continue in the study. The source document indicates that subject [redacted] completed study visit 3 by phone on January 11, 2002. However, the source document also states that the subject refused to have blood drawn on that date. In your written response, you stated that the subject finished the medications as directed, completed both study visits 2 and 3 on January 11, 2002, and had blood drawn on that date. Your response does not explain these discrepancies.

f. For subjects [redacted] and [redacted] the CRF indicates that study visit 3 was conducted as an office visit on 2/6/02, 2/6/02, 2/13/02, and 2/22/02, respectively; however, source documentation indicates that each subject was telephoned. In your written response, you acknowledged that visits should have been recorded as telephone contacts and not office visits.

g. The concomitant medications recorded on CRFs for a number of subjects were not consistent with source documents. For example:

- Subject [redacted] CRF lists 10 drugs at baseline; a source document lists two.
- Subject [redacted] CRF lists 10 drugs; a source document lists 18 drugs.
- Subject [redacted] concomitant medications listed in CRF do not match source documents.
- Subject [redacted] CRF lists 6 drugs for duration of study; a source document lists over 20 medications.
- Subject [redacted] CRF lists only Xanax for duration of study, a source document shows additional drugs.

We find the explanation for the inadequacy and inaccuracy of subject records in your October 7, 2003, written response to FDA to be unacceptable.

3. You failed to ensure the study was conducted according to the investigational plan [21 CFR 312.60].

The protocol required that blood samples for ALT, AST, total bilirubin and alkaline phosphatase be obtained at study visits 1 and 2. For subject [redacted] (visit 1), subject [redacted] (visit 1), and subject [redacted] (visit 2), laboratory results for required blood tests were missing. In your October 7, 2003, written response you state that lab results were

missing and subsequently found, or drawn blood was lost. We find this explanation for the missing required blood tests to be unacceptable.

4. **You failed to adequately document informed consent [21 CFR 50.27(a)].**

   Informed consent must be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. Our investigation found that the informed consent document for subjects [redacted] and [redacted] were signed but not dated by the subjects. In your response, you stated that these subjects did not date the consent when they signed, therefore, your assistant recorded the date on the consent document. We find this explanation unacceptable.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical studies of investigational products. It is your responsibility to ensure adherence to each requirement of the law and relevant regulations.

On the basis of the above listed violations, FDA asserts that you have submitted false information to the sponsor or FDA in a required report and repeatedly or deliberately failed to comply with the cited regulations, which placed unnecessary risks to human subjects and jeopardized the integrity of data, and the FDA proposes that you be disqualified as a clinical investigator. You may reply to the above stated issues, including an explanation of why you should remain eligible to receive investigational products and not be disqualified as a clinical investigator, in a written response or at an informal conference in my office. This procedure is provided for by regulation 21 CFR 312.70.

Within fifteen (15) days of receipt of this letter, write or call me at (301) 594-0020 to arrange a conference time or to indicate your intent to respond in writing.

Should you choose to respond in writing, your written response should be forwarded within thirty (30) days of receipt of this letter.

Your reply should be sent to:

Leslie K. Ball, M.D.
Acting Director
Division of Scientific Investigations, HFD-45
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
7520 Standish Place, Room # 103
Rockville, Maryland 20855

Should you request an informal conference, we ask that you provide us with a full and complete explanation of the above listed violations. You should bring with you all pertinent documents, and a representative of your choice may accompany you. Although the conference is informal, a transcript of the conference will be prepared. If you choose to proceed in this manner, we plan to hold such a conference within 30 days of your request.

At any time during this administrative process, you may enter into a consent agreement with FDA regarding your future use of investigational products. Such an agreement would terminate this disqualification proceeding. Enclosed you will find a proposed agreement between you and FDA.

The FDA's Center for Drug Evaluation and Research (the Center) will carefully consider any oral or written response. If your explanation is accepted by the Center, the disqualification process will be terminated. If your written or oral responses to our allegations are unsatisfactory, or we cannot come to terms on a consent agreement, or you do not respond to this notice, you will be offered a regulatory hearing before FDA, pursuant to 21 CFR 16 (enclosed) and 21 CFR 312.70. Before such a hearing, FDA will provide you notice of the matters to be considered, including a comprehensive statement of the basis for the decision or action taken or proposed, and a general summary of the information that will be presented by FDA in support of the decision or action. A presiding officer free from bias or prejudice and who has not participated in this matter will conduct the hearing. Such a hearing will determine whether or not you will remain entitled to receive investigational products.

You should be aware that neither entry into a consent agreement nor pursuit of a hearing precludes the possibility of a corollary judicial proceeding or administrative remedy concerning these violations.

Sincerely yours,

{See appended electronic signature page}

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

Enclosures:
#1 - 21 CFR 312.70
#2 - 21 CFR 16
#3 - Consent Agreement

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
8/29/2007 11:05:06 PM