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

AUG 24 2005

Jeffrey L. McLeod, M.D.
5001 W. Village Green Drive
Suite 108
Midlothian, Virginia 23112

Dear Dr. McLeod:

Between July 24, 2003 and August 6, 2003, Ms. Candice C. Mandera, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review the conduct of the following clinical study in which you participated as the clinical investigator:

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, Ketek®, was sponsored by Aventis Pharmaceuticals.

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.

At the conclusion of the inspection, Ms. Mandera presented you the Form FDA 483, Inspectional Observations.

We have evaluated the inspection report, the documents submitted with that report and pertinent information obtained by the Agency. FDA's Center for Drug Evaluation and Research (the Center) believes that you have repeatedly or deliberately violated regulations governing the proper conduct of clinical studies involving investigational new drugs as published under Title 21, Code of Federal Regulations (CFR), Part 312 (copy enclosed) and that you submitted false information in a required report to FDA or the sponsor.

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 312.70.

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

1. **You failed to obtain legally effective informed consent from human subjects enrolled in the above-referenced study [21 CFR 312.60, 21 CFR 50.20].**

An investigator is responsible for obtaining the informed consent of each human subject to whom study drug is administered in accordance with the requirements of 21 CFR Part 50 (see 21 CFR 312.60). In particular, 21 CFR 50.20 requires that "[a]n investigator shall seek such consent only under circumstances that provide the prospective subject or the [subject's legally authorized] representative sufficient opportunity to consider whether or not to participate . . . ." Between December 12, 2001 and January 23, 2002, you enrolled 30 subjects in Protocol [ ]. However, you failed to obtain informed consent for any subject prior to their enrollment. For several of those subjects, informed consent was apparently never obtained. For others, you sought and obtained informed consent after the subjects had enrolled and been treated with study drug. Any informed consent obtained after study enrollment is not legally effective informed consent because it was not obtained under circumstances that provided the subject sufficient opportunity to consider, prospectively, whether or not to participate in the study. We note the following:

a. You failed to obtain informed consent for seven subjects (subjects 3, 11, 15, 16, 21, 24, and 25).

b. For six subjects (subjects 5, 7, 8, 14, 17, and 19), you provided FDA investigators informed consent documents that were signed and dated by the subjects after they had completed the study.

c. For 17 subjects (subjects 1, 2, 4, 6, 9, 10, 12, 13, 18, 20, 22, 23, 26, 27, 28, 29, and 30), you provided FDA investigators informed consent documents in which the subject signatures were backdated to make it appear that informed consents were obtained from the subjects prior to their enrollment in the study (see item 2a below).

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

You falsified dates accompanying signatures on informed consent documents to make it appear as though informed consent was obtained from subjects prior to their enrollment in the study. For 23 subjects you used an informed consent document template provided by the study's Institutional Review Board (IRB), [ ] that you received on March 4, 2002, well after you had stopped enrolling subjects in this study. The copies of the template used for these subjects all have "03/04/2002 17:20 FAX [ ] in the upper left-hand corner [ ] is the fax number for [ ] We are aware that you contacted the sponsor's study monitor on 3/04/02 and informed her that you had never received your IRB approval packet with the informed consent document, and that you had enrolled 30 subjects without using the IRB-approved informed consent document. We are also aware that the study monitor contacted the IRB concerning your failure to obtain informed consent for study subjects and the IRB then faxed you the packet that same day,

including the template of the informed consent document that you used for these 23 subjects. The informed consent documents for 22 of the 23 subjects contain at least one signature (either subject signature or your signature as the person who obtained the informed consent) with a date that precedes the date you received the informed consent template. Specifically,

a. On 17 informed consent documents (subjects 1, 2, 4, 6, 9, 10, 12, 13, 18, 20, 22, 23, 26, 27, 28, 29, and 30), the subject's signature was dated prior to 3/04/02. You acknowledged that you backdated the signature for subject 27, and it appears that the handwriting for the signature dates on the informed consent documents for subjects 2, 6, 12, 28, and 29 is the same as the handwriting for the date on subject 27's informed consent document (i.e., your handwriting). Subject 6 also confirmed that she did not write the date on her informed consent document. A member of your staff told the FDA Investigator that you instructed her to backdate the informed consent signatures for subjects 4, 8, 9, 13, 18, 22, 23, and 30. The monitoring report by the contract research organization[ ] dated 3/25/02, indicates that 21 subjects had not yet signed their informed consent documents as of 3/21/02 (the date of the monitoring visit).

b. On 13 informed consent documents (subjects 7, 9, 10, 12, 14, 17, 19, 22, 23, 27, 28, 29, and 30), your signature, as the person who obtained the informed consent, is dated prior to 3/04/02.

3. **You failed to adhere to the protocol [21 CFR 312.60].**

a. The protocol required clinical laboratory tests (ALT, AST, total bilirubin, alkaline phosphatase) to be done at Visit 1 (pre-therapy visit) and Visit 2 (post-therapy visit). There is no documentation to show that such tests were conducted at Visit 1 for subjects 20, 21, 23, and 27. There is no documentation to show that such tests were conducted at Visit 2 for subjects 3, 5, 13, 16, 17, 18, 22, and 27.

b. As part of the safety evaluation for the study, the protocol required the investigator to document adverse events and determine whether any documented events were serious or of "special interest" as that term is defined in the protocol. For subjects 17 and 22 you had laboratory tests done (serum potassium and magnesium) on 2/07/02 and 2/05/02, respectively, to evaluate what was identified on the laboratory report as a "Cardiac Adverse Event." However, you did not record these adverse events on the Case Report Form (CRF). For each of these subjects, the CRF indicates that the subject experienced no adverse events during the trial.

c. To document which study drug subjects received, the protocol required that the tear-off labels on the cartons of the study drugs (telithromycin or the comparator, amoxicillin/clavulanate) be removed from the cartons and placed in the designated field in the CRF before the drugs were dispensed to study subjects. For subjects who received study drug, you failed to remove the tear-off labels and place them in the CRFs. For these subjects, it cannot be determined which study medication was dispensed.

d. The protocol required that women of childbearing potential have a urine pregnancy test at Visit 1 to confirm that they were not pregnant before taking study medication. However, there is no documentation to show that required urine pregnancy tests were done at visit 1 for subjects 11, 14, 17, 18, 21, and 30.

e. The protocol excluded individuals with a hypersensitivity to beta-lactam classes of antibiotics. Subject 6 was enrolled despite a documented allergy to penicillin, a beta-lactam antibiotic.

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

On the basis of the above listed violations, the Center asserts that you have repeatedly or deliberately failed to comply with the cited regulations and submitted false information to FDA or the sponsor in a required report. The Center proposes that you be disqualified as a clinical investigator. You may reply in writing or at an informal conference in my office 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. 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. Your written response must be forwarded within thirty (30) days of receipt of this letter. Your reply should be sent to:

Joanne L. Rhoads, M.D., MPH
Director
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
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 all pertinent documents with you, and a representative of your choosing 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 the Center 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 the Center.

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,

Joseph P. Saleski for

Joanne L. Rhoads, M.D., MPH
Director
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research

Enclosures:
#1 - 21 CFR 312.70
#2 - 21 CFR 16
#3 - 21 CFR 50
#4 - Agreement