DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

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

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Keith J. Pierce, M.D.
Michigan Institute of Medicine
38525 Eight Mile Road
Livonia, MI 48152

Dear Dr. Pierce:

Between November 4 and 25, 2003, Ms. Lisa P. Oakes and Ms. Catherine V. Quinlan, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review the conduct of the following clinical studies sponsored by Aventis Pharmaceuticals, Inc:

1. Protocol HMR3647A/3014, 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"

2. Protocol (b) (4), entitled "(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.

At the conclusion of the inspection, FDA investigators presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. We have reviewed the inspection report, the documents submitted with that report, other pertinent information obtained by the Agency, and your written responses to the Form FDA 483 dated December 29, 2003. We do not find your response to be acceptable in addressing the matters under complaint, which are described below.

Based on our evaluation of information obtained by the Agency, we believe that you have repeatedly or deliberately submitted false information to the sponsor or FDA 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 312.70 (copy enclosed).

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

   Protocol (b) (4) specified that on Day 1 [Baseline/Pre-therapy Visit], a sinus X-ray was to be taken. The sinus X-ray was to be performed before a subject's inclusion in the study, to confirm the presence of air fluid level, total opacity, or mucosal thickening $\geq$ 10 mm. While the subject could be enrolled into the study based on the investigator's evaluation of the sinus X-ray, the sinus X-ray was to be reviewed by a radiologist to confirm the diagnosis of (b) (4) The sinus X-ray was to be repeated between Day 17 and Day 24 [Post-therapy/Test of Cure (TOC) Visit] and, per protocol, was also to be reviewed by a radiologist. The same radiological modality (e.g., sinus X-ray view) was to be used at the Baseline/Pre-therapy Visit and Post-therapy/Test of Cure Visit of each patient.

   You informed FDA investigators that you created the "Radiologist Interpretation" worksheet used in the study which you used to qualify subjects for the study. This worksheet contained information related to the view of the X-ray (Section 1); a choice of three interpretations for the X-ray (presence of air fluid level, total sinus opacity, and/or mucosal thickening in mm - Section 2); a line for "Radiologist Name" (i.e., the name of the radiologist reviewing the X-ray); and a line for "Radiologist signature and date" for the radiologist to sign and date. You stated that based on your information, either you or the research coordinator completed Sections 1 and 2 on the worksheet, and wrote Dr. (b) (4) 's name on the line for "Radiologist name." The radiologist, Dr (b) (4) , then only needed to sign the worksheet.

   You further informed FDA investigators that the "Radiologist Interpretation" worksheets and the X-rays were then sent via courier to Dr. (b) (4) 's office a couple of times a week. After being read, both the worksheets and the X-rays were returned to your office. You noted that you did not receive original dictated radiologist reports with the X-rays that were sent back from Dr (b) (4) . You further informed FDA investigators that you gave parts but not all of the protocol to Dr (b) (4) to review; that you walked through the protocol with Dr. (b) (4) ; and that Dr (b) (4) was supposed to call you if a subject should not be in the study based on the review of the X-ray.

In addition, you informed FDA investigators that after the July 2003 monitoring visit, when the study monitor raised questions about the signatures found on the "Radiologist Interpretation" worksheets, you had Dr. (b) (4) re-sign the worksheets on August 6, 2003. You then later had Dr. (b) (4) reread the X-rays on August 13, 2003, so there would be no questions. The reread X-rays were dictated and dated either August 13, 2003, or August 22, 2003.

We found significant discrepancies in the information that you provided to FDA investigators. For example:

a. In discussions with FDA investigators, Dr. (b) (4), Medical Director for (b) (4) (hereafter referred to as (b) (4)), refuted your explanation of the events that transpired in relation to the study X-rays and the signatures on the "Radiologist Interpretation" worksheets. Specifically:

   i. Dr. (b) (4) noted that prior to August 2003, he had no formal agreement with you to perform interpretation of X-rays for your research studies. He noted that the X-rays from Protocol (b) (4) provided by you were not identified as X-rays for research subjects and were processed like all other diagnostic interpretations, which included the creation of radiologic dictation reports.

   ii. Dr. (b) (4) noted that on or about August 6, 2003, when Aventis representatives visited his site, he informed them that he had never seen your "Radiologist Interpretation" worksheets, and that the signature on each of the forms was not his. He re-affirmed to FDA investigators that the original signature on the line "Radiologist signature and date" of each "Radiologist Interpretation" worksheet was not his.

   iii. Dr. (b) (4) noted that after the Aventis visit, you informed him that someone in your office had completed and signed the "Radiologist Interpretation" worksheets, based on dictation letters from his office. You then asked Dr. (b) (4) to sign the "Radiologist Interpretation" worksheets, which he did on August 6, 2003. Dr. (b) (4) then stated that he had informed you that he needed to reread the X-rays. Dr. (b) (4) noted that you brought the X-rays to his office and stood with him as he did his interpretations and dictation for the 22 subjects screened for Protocol (b) (4). Dr (b) (4) further stated that his interpretations were then transcribed onto your letterhead on August 13 and 22, 2003.

b. During a July 29-31, 2003, monitoring visit, you informed Aventis study monitors that with respect to the "Radiologist Interpretation" worksheets, your site staff only completed the header, and Dr. (b) (4) and/or his staff completed the X-ray results and signed and dated the worksheet. In addition, the monitoring report noted that you called Dr. (b) (4) at the time of the visit and informed the monitors that Dr. (b) (4) has stated that he "…reviewed all sinus X-rays and signed all sinus X-ray worksheets."

Subsequent to the monitoring visit, in a letter dated August 13, 2003, you claimed to Aventis Pharmaceuticals that you had reviewed your standard operating procedures and followed your procedures properly. The letter further stated that you had decided to have Dr. (b) (4) re-sign and reread all X-ray films and confirm the initial reports, which you then faxed to the sponsor.

c. Numerous inconsistencies were identified in review of the information on your "Radiologist Interpretation" worksheets and your log of X-rays sent to (b) (4), and the dictated radiologist reports from (b) (4), raising significant questions regarding whether several subjects you enrolled actually qualified for the study. For example:

i. For several subjects, the date noted on the "Radiologist Interpretation" worksheet as the date the radiologist initially signed the worksheet preceded the date of receipt of the X-ray by (b) (4) and/or the date of the initial X-ray readings by (b) (4) radiologists. For example:

Subject No.	Visit Type	Date of Visit	Initial date signed by radiologist, as noted on "Radiologist Interpretation" worksheet	Date X-ray logged, as received by (b) (4)	Date of initial dictated radiologist's report
001	Baseline	4/08/03	4/10/03	4/10/03	4/14/03
	TOC	4/25/03	4/27/03	4/29/03	4/30/03
002	Baseline	4/11/03	4/12/03	4/15/03	4/16/03
006	Baseline	5/15/03	5/17/03	5/22/03	5/24/03
007	Baseline	5/16/03	5/18/03	5/22/03	5/24/03
020	Baseline	6/27/03	6/30/03	7/01/03	7/02/03
021	Baseline	7/10/03	7/12/03	7/15/03	7/16/03

Given the findings noted where the date on the "Radiologist Interpretation" worksheet was signed prior to the date (b) (4) received the X-ray and/or the date of the initial dictated radiologist's report, your statements made to FDA investigators that Dr. (b) (4) initially reviewed and signed all the worksheets were shown to be false by the documents.

ii. For several subjects, the original radiologist's interpretation of the X-ray did not confirm the findings noted in "Radiologist Interpretation" worksheets. For example:

Subject No.	Visit Type	Date of Visit	"Radiologist Interpretation" Worksheet finding	Date of initial dictated radiologist's rpt.	Initial dictated radiologist's report finding
001	Baseline	4/8/03	Air fluid level left & right; mucosal thickening left & right 12 mm	4/14/03	Normal sinuses

Subject No.	Visit Type	Date of Visit	"Radiologist Interpretation" Worksheet finding	Date of initial dictated radiologist's rpt.	Initial dictated radiologist's report finding
002	TOC	4/28/03	Resolved [(b) (4)]	4/30/03	(b) (4) bilaterally
004	TOC	5/05/03	100% [resolved (b) (4)	5/07/03	Chronic (b) (4)
009	Baseline	5/20/03	Total sinus opacity (b) (4) left and right	5/24/03	Normal paranasal sinuses
010	Baseline	5/27/03	Mucosal thickening 12 mm bilateral	5/30/03	Visualized sinuses are clear
011	Baseline	5/28/03	Air fluid level left and right; mucosal thickening 13 mm bilateral	5/30/03	No evidence of mucosal thickening and air fluid level. Negative paranasal sinuses.
012	Baseline	5/29/03	Mucosal thickening 14 mm left 10 mm right	6/04/03	Paranasal sinuses are clear
013	TOC	6/23/03	Resolved [(b) (4)]	6/25/03	Chronic (b) (4)
018	TOC	7/11/03	Resolved [(b) (4)]	7/16/03	Chronic (b) (4)

While the rereading dictations of the X-rays performed by Dr. (b) (4) in August 2003 generally matched the findings noted on the "Radiologist Interpretation" worksheets, Dr (b) (4) informed FDA investigators there may have been bias in his reread of the X-rays. Specifically, Dr. (b) (4) stated that you were standing with him while he reread and dictated each X-ray; that the two of you discussed the interpretations as they were being made; that you showed him where the signs of (b) (4) were if he did not immediately see them; and that you told him the entry criteria for each subject.

iii. Information was found on the "Radiologist Interpretation" worksheets for the following subjects suggesting that X-rays had been reviewed and interpreted by a radiologist:

Subject No.	Visit Type	Date of Visit	Reported date that radiologist signed "Radiologist Interpretation" Worksheet
003	Baseline	4/14/03	4/16/03
004	Baseline	4/14/03	4/17/03
017	Baseline	6/19/03	6/23/03
019	Baseline	6/26/03	Not dated initially

However, in review of your log of X-rays sent to (b) (4) between April and August 2003, there was a line through the X-rays for Subjects 003, 004, and 017 for the dates noted above, implying that these X-rays had not been sent to (b) (4). There was no evidence found that the X-ray for Subject 019 was sent to (b) (4), as stated in your log of dictated X-rays. Our review of the (b) (4) log of all X-rays received and interpreted from your office, as well as the (b) (4) dictated reports for subjects enrolled into the study, leads us to conclude that these subjects' X-rays were not received and interpreted by (b) (4) prior to the date noted on your "Radiologist Interpretation" worksheets.

Based on FDA's investigation, we have determined that the "Radiologist Interpretation" worksheets that you created to document subject eligibility and the results of study treatment, initially contained the falsified signature of Dr (b) (4) and falsely represented that Dr (b) (4) performed all X-ray interpretations for the subjects enrolled at your site.

FDA notes that you submitted the "Radiologist Interpretation" worksheet to the sponsor. In addition, you included information from the worksheets in CRFs submitted to the sponsor.

We note that Dr (b) (4)'s belated August 6, 2003, signature on the "Radiologist Interpretation" worksheets and his "rereadings" of sinus X-rays on either August 13 or August 22, 2003, do not change the fact that you submitted false data to the sponsor. Falsification of these X-ray assessments resulted in false information submitted to the sponsor in support of the study. Submission of false information to the sponsor in a required report is a violation of 21 CFR 312.70(a).

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

a. For Protocol (b) (4):

i. The protocol excluded subjects who were receiving other medications, including systemic antimicrobial agents that could interfere with the evaluation of drug efficacy or safety. In addition, the protocol stated that no oral or parenteral concomitant antibiotic treatments were permitted for the duration of study medication. Patients receiving oral or parenteral antibiotic treatments that could not be discontinued were not eligible for inclusion in the study, and patients requiring such antibiotic treatments other than the study medication during the study had to be withdrawn from the study and from the study medication. Subject 005's source records, however, showed that the subject was given Rocephin, an antibiotic, on May 7, 2003, the date of study Visit 1.

ii. The protocol specified that patients who had received treatment with other systemic (oral or parenteral) antibiotics within 14 days prior to enrollment were to be excluded from the study. Source records indicated that on June 16,

2003, Subject 018 was prescribed a 10-day regimen of ciprofloxacin ("Cipro 500 mg BID #20"). However, Subject 018 was enrolled into Study (b) (4) on June 23, 2003.

In your written response dated December 29, 2003, you stated that the study had not finished by the time of FDA's inspection of your site, and that the charts had not been reviewed by the clinical research associates. You provided notes to files stating that Subject 005 was never given the Rocephin shot, and that Subject 018 was not given ciprofloxacin. These notes to files were dated December 1, 2003, and December 3, 2003, respectively.

Your response is inadequate. These notes to files were written after the FDA inspection, when you were informed of these findings. With respect to Subject 005, you informed the FDA investigators during the inspection that since the word *Rocephin* was circled, this meant that the injection was ordered and given to the subject. This contradicts your statement made in the note to file submitted in your written response. For Subject 018, your source records clearly had handwritten information showing that the subject was prescribed ciprofloxacin.

b. Protocol HMR3647A/3014 specified that all treatments being taken by the subjects on their entry into the study or at any time during the study, in addition to the investigational product, are regarded as concomitant treatments and must be documented on the appropriate pages of the case report form (CRF). You failed to report on the CRF all concomitant treatments noted in the source records. Examples include the following:

Subject	Date of visit	Medication
123	1/07/02	Cerumenex, Coriticosporin
165	1/26/02	Aleve
174	2/11/02	Nebulizer treatment

In your written response, you stated that the sponsor informed you with respect to Subjects 123 and 165 that over-the-counter medications did not need to be included in the concomitant medications list. With respect to Subject 174, you concurred that this treatment was missed on the concomitant list.

Your response concerning Subjects 123 and 165 is inadequate. Specifically, the protocol did not state that over-the-counter medications should not be listed on the CRF. In addition, you provided no supporting documentation that the sponsor informed you that over-the counter medications need not be included in the concomitant medications list.

3. 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)].

a. For Protocol (b) (4) :

i. A check mark in the "No" box was found on Subject 004's Day 1 – Baseline/Pre-therapy Visit CRF in response to the question, "Has the subject previously participated in any (b) (4) study?" Source records, however, showed that this subject had previously participated in Protocol (b) (4) .

ii. A check mark in the "No" box was found on Subject #018's Day 1 – Baseline/Pre-therapy Visit CRF in response to the question, "Previous (b) (4) episodes in the last year?" However, handwritten progress notes indicated that this subject had been diagnosed with (b) (4) on June 24, 2002, and December 24, 2002. Both dates were within one year of Visit 1 (June 23, 2003).

In your written response, you stated that the study was not closed until December 20, 2003, and that the source documents and CRFs still needed to be reviewed by the Aventis clinical research associate and your Site Coordinator. You submitted notes to files in reference to these findings. With respect to Subject 004, you confirmed this finding. With respect to Subject 018, the note to file dated December 1, 2003, stated that the subject was given a prescription for the Cipro 500 mg BID#20, but never had the prescription filled and never took any of the medication.

Your response concerning Subject 018 is inadequate. Specifically, your responses did not adequately address the findings related to this subject. In addition, the notes to file submitted as a part of your written response was written after the FDA inspection during which this finding was identified to you.

b. For Protocol HMR3647A/3014:

i. The Visit 2 source document states that Subject 008 took study drug November 8-18, 2001. The CRF dated November 26, 2001, states that the subject took the study drug from November 8-10, 2001.

ii. The Visit 1 source document shows that Subject 161 had a history of asthma and diabetes. These two conditions are not included on the medical history section of the CRF.

iii. The CRF showed that Subjects 148 and 152 met eligibility criteria for this study because they had acute sinusitis. FDA's review of the TREAT Study Visit 1 records, however, failed to verify that these subjects met the inclusion criterion of having a clinical diagnosis of community-acquired pneumonia, acute exacerbation of chronic bronchitis, or acute sinusitis.

In your written response, you stated that for Subject 008, the date on the source document was lined through and changed to November 10, 2001, for the end of study, and that the lining through and initialing were done on April 16, 2002. You concurred with the findings noted for Subjects 148, 152, and 161.

Your response concerning Subject 008 is inadequate. In review of the information you provided, your response could not be verified.

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 failed to protect the rights, safety, and welfare of subjects under your care; repeatedly or deliberately submitted false information to the sponsor; 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 301-796-3150 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.
Director
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5342
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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.

To enter into the enclosed consent agreement with FDA, thereby terminating this disqualification proceeding, you must:

(1) initial and date each page of this Agreement;
(2) sign and date the last page of this Agreement; and
(3) return this Agreement initialed, signed, and dated to the signer below.

A copy of the fully executed Agreement will be mailed to you.

Sincerely yours,

{See appended electronic signature page}

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

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

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

/s/

LESLIE K BALL
03/17/2010