C/E

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)

FEB 24 2003

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Harrison F. Aldrich, D.O.
Unity Medical Center
One Main Street, P.O. Box 178
Unity, Maine 04988

Dear Dr. Aldrich:

Between July 24 and 28, 2000, Ms. Ellen P. Madigan and Ms. M. Patricia Murphy, representing the Food and Drug Administration (FDA), conducted an inspection of the following clinical studies in which you participated as the investigator of record:

Protocol # (b) (4) titled, " (b) (4) ," sponsored by (b) (4) .

Protocol #CEF97-011 titled, "Comparative Safety and Efficacy of Cefditoren Pivoxil and Cefadroxil Monohydrate in the Treatment of Patients with Uncomplicated Skin and Skin Structure Infection," sponsored by TAP Pharmaceuticals.

Protocol #D96-026 titled, "Prospective, Randomized, Double Blind, Multi-Center Comparison of the Safety and Efficacy of Bay 12-8039 400 mg QD for 10 Days versus Clarithromycin 500 mg BID for the Treatment of Patients with Community Acquired Pneumonia," sponsored by Bayer Corporation.

Protocol #HMR3647A/3009 titled, "A Double-Blind, Multicenter, Randomized, Active-Controlled, Two-Arm Parallel-Group Comparative Study of the Efficacy and Safety of Oral HMR 3647 (800 mg once daily) for 7 to 10 Days Versus Oral Trovafloxacin (200 mg once daily) for 7 to 10 Days in the Treatment of Community-Acquired Pneumonia in Adults," sponsored by Hoechst Marion Roussel Pharmaceuticals.

This inspection is part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects in those studies are protected.

At the conclusion of the inspection our personnel presented and discussed with you the items listed on the Form FDA 483, Inspectional Observations. We have reviewed your signed affidavit dated July 28, 2000. We note that in the affidavit you concur with the inspectional observation that you enrolled five subjects who were known diabetics in violation of the protocol, and that for four of five subjects you did not report their history of diabetes in their study records. In addition, you also state that you "will probably not participate in any more clinical trials in the future."

Based on our evaluation of the inspection report and the documents submitted with that report, FDA's Center for Drug Evaluation and Research (the Center) believes that you have repeatedly and/or deliberately violated regulations governing the proper conduct of clinical studies involving investigational new drugs as published under Title 21 of the Code of Federal Regulations part 312 (21 CFR part 312, copy enclosed), and that you submitted false information to 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 list of the violations follows. The applicable provisions of the CFR are cited for each violation.

1. **You submitted false data to the sponsor [21 CFR 312.70(a)] and failed to adhere to the study protocol [21 CFR 312.60].**

   For each of the study subjects identified below, you submitted false data to the sponsor. For most of the identified subjects you also failed to adhere to the study protocol; in these cases, your submission of false data concealed that failure.

   Protocol # (b) (4)

   a. For subject (b) (6) (#1107), you falsely reported in the case report form (CRF) that this subject was not treated with azithromycin within two weeks of study drug administration. However, your private practice records show that you administered Zithromax (azithromycin) to subject (b) (6) within 14 days of study drug administration. Thus, you enrolled this subject in violation of the protocol exclusion criterion (section 4.2.9), which excluded subjects who had treatment with azithromycin within 2 weeks prior to study drug administration. Your submission of the false information in the CRF concealed that failure to follow the study protocol.

b. For subject (b) (6) (#1541), you falsely reported in the case report form (CRF) that this subject did not have any infection necessitating the use of concomitant antibiotics, and that this subject did not receive concurrent nasal steroid therapy. However, your private practice records show that this subject had acute otitis media on the day of study enrollment, and that on the same day you administered Ceftin (cefuroxime axetil) and Flonase (a nasal steroid spray). Thus, you enrolled this subject in violation of the protocol exclusion criteria (sections 4.2.7 and 4.2.18), which excluded subjects who had an infection necessitating the use of concomitant antibiotics, and subjects receiving or likely to receive nasal steroid therapy. Your submission of the false information in the CRF concealed that failure to follow the study protocol.

c. For subjects (b) (6) (#1452), (b) (6) (#1453), (b) (6) (#1454), (b) (6) (#1455), (b) (6) (#1456), and (b) (6) (#1542), you falsely reported in their respective CRFs that the duration of sinus infection symptoms lasted > 7 days and ≤ 4 weeks. However, the duration of sinus infection symptoms that you recorded in the clinic charts for each of these subjects show that their symptoms lasted for less than seven days. Thus, you enrolled these subjects in violation of the protocol inclusion criterion (section 4.1.1), which required these subjects have sinus infection symptoms for > 7 days and ≤ 4 weeks. Your submission of the false information in the CRF concealed that failure to follow the study protocol.

d. For subject (b) (6) (#1107) you falsely reported in the CRF that on 4/10/98 a follow-up office visit was not necessary. However, your private practice records show that the subject visited your clinic on 4/10/98 primarily because of "difficulty in breathing," which demonstrates the necessity of the visit.

e. For subjects (b) (6) (#1107) and (b) (6) (1456) you failed to report in the Concurrent Medications page of their respective CRFs that they were treated with non-study antibiotics before their final follow-up visit. Your private practice records show that prior to the final follow-up visit you administered Bactrim DS (trimethoprim and sulfamethoxazole double strength) to subject (b) (6) and Ceftin (cefuroxime axetil) to subject (b) (6). Your submission of the false information in the CRF concealed the fact that these subjects received treatment with a non-study antibiotic before their respective final follow-up visit.

Protocol #CEF97-011

f. For subjects (b) (6) (#5231), (b) (6) (#5234), (b) (6) (#5720), and (b) (6) (#5916), you falsely reported in their respective CRFs that they did not have Diabetes Mellitus. Your private practice records and/or laboratory reports for these subjects show that they did have Diabetes Mellitus. Thus, you enrolled these subjects in violation of protocol section 4.2.19, which required exclusion of subjects with Diabetes Mellitus. Your submission of the false information in the CRF concealed that failure to follow the study protocol.

g. For subject (b) (6) (#5720) you falsely reported in the CRF that the subject did not receive systemic antibiotic therapy within 7 days prior to study drug administration. Your private practice records show that you administered Bactrim DS to this subject three days prior to starting the study drug. Thus, you enrolled the subject in violation of protocol section 4.2.6, which required exclusion of subjects treated with a systemic antibiotic within seven days prior to study drug administration. Your submission of the false information in the CRF concealed that failure to follow the study protocol.

h. For subject (b) (6) (#5234) you falsely reported the following:

i. You reported in the CRF that this subject did not meet exclusion criteria outlined in sections 4.2.4, 4.2.5, and 4.2.13 of the protocol, specifically excluding subjects with a site of infection requiring an incision and drainage of the infected areas or with an infection necessitating the use of a concomitant oral antibiotic therapy or systemic antimicrobial therapy. However, your private practice records for this subject show that on 3/16/99, study Day 1, you performed an incision and drainage of the abscess on the right flank area and administered Keflex to the subject. Thus, you enrolled this subject in violation of the protocol. Your submission of the false information in the CRF concealed that failure to follow the study protocol.

ii. You reported in the CRF that an office visit was not necessary for this subject on 3/19/99, and that the subject reportedly was "feeling better." However, your private practice records show that the subject visited your clinic on 3/19/99 to recheck his abscess and diabetes, and that at that time you recommended the continuation of treatment with Keflex and ichthammol ointment in addition to the study drug. Your submission of the false information in the CRF concealed the fact that the subject made an unscheduled office visit and continued to receive treatment with a non-study antibiotic before the subject's final follow-up visit.

2. Failure to provide FDA personnel with access to copy and verify study records and reports, in violation of 21 CFR 312.68.

Protocol # (b) (4)

a. The x-rays films for all the 27 subjects enrolled in the study were not available during the inspection.

Protocol #CEF97-011

b. The private practice records (source documents) for subjects (b) (6) (#5916) and (b) (6) (#5715), were not available during the inspection.

3. Failure to report adverse events, in violation of 21 CFR 312.64(a) and (b).

Protocol #HMR3647-3009

You failed to report in the CRF that subject (b) (6) (#003) experienced "occasional dizzy spells," as recorded in the private practice records that you maintained for this subject corresponding to the subject's study visit 3 on 5/14/99.

4. Failure to maintain adequate and accurate records, in violation of 21 CFR 312.62(b) and (c).

Protocol # (b) (4)

a. For subjects (b) (6) (#1031), (b) (6) (#1033), (b) (6) (#1034), (b) (6) (#1036), (b) (6) (#1085), and (b) (6) (#1086), data were inserted into their study related clinic charts (source documents) without any explanation, date, or initial, to help determine why, when and from where such data were recorded, and who recorded such data.

b. For subjects (b) (6) (#1033), (b) (6) (#1035), (b) (6) (#1036), (b) (6) (#1085), (b) (6) (#1086), (b) (6) (#1087), (b) (6) (#1108), (b) (6) (#1541), (b) (6) (#1543), and (b) (6) (#1544), there was no source documentation to verify that the duration of each subject's sinus infection symptoms lasted >7 days and ≤ 4 weeks, as required by the protocol.

Protocol #CEF97-011

c. For subject (b) (6) (#5234)

i. You failed to report in the medical history section of the CRF for Visit 1 on 3/16/99, that the subject had acute urethritis, angina, dorsal strain, somatic dysfunction, and constipation. These conditions were recorded in the private practice records dated 3/16/99 that you maintained for this subject.

ii. You failed to report in the concurrent medications section of the CRF that you also administered Keflex, Glucotrol XL, Norvasc, Pyridium, allopurinol, and applied ichthammol ointment. These treatments were recorded in the private practice records that you maintained for this subject.

d. For subject (b) (6) (#5720)

i. You failed to report in the medical history section of the CRF for Visit 1 on 12/18/98, that the subject had acute cystitis, acute urethritis, congestive heart failure, chronic obstructive pulmonary disease, angina, and renal compromise. These conditions were recorded in the private practice records that you maintained for this subject.

ii. You reported in the concurrent medications section of the CRF that this subject was not administered any medications other than the study drug from 30 days prior to the Pre-Therapy Visit through the Final Visit. Your private practice records show that at least three days prior to starting study drug, you administered to this subject Bactrim DS, Glucophage, Glucotrol, hydrochlorothiazide, Zoloft, Theophylline, Digoxin, Vasotec, Nitroglycerin, Servent, Pyridium and Voltaren.

Protocol #D96-026

e. For subject (b) (6) (#437), you did not report in the study specific clinic charts all the medications administered to the subject on 12/5/97, and 12/8/97. Specifically, you did not report the administration of Biaxin on 12/5/97 and Rocephin IM on 12/8/97, that were recorded in the private practice records you maintained for this subject.

5. Failure to obtain legally effective informed consent for several subjects, in violation of 21 CFR 50.27(a).

Protocol # (b) (4)

a. A review of the consent forms show that at least five subjects [(b) (6) (#1031), (b) (6) (#1032), (b) (6) (#1036), (b) (6) (#1455), and (b) (6) (#1616)] did not date their signature when they signed their consent form. During the FDA inspection, your study coordinator admitted to the FDA investigators that he recorded the date of signature on the consent form for several subjects.

Protocol #CEF97-011

b. A review of the consent forms show that at least two subjects [(b) (6) (#5231) and (b) (6) (#5556)] did not date their signature when they signed their consent form. During the FDA inspection, your study coordinator admitted to the FDA investigator that he recorded the date of signature on the consent form for several subjects.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical studies 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 and deliberately failed to comply with the requirements of 21 CFR 312 and have submitted false information to the sponsor. 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 be 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) calendar 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 response 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 the 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 had not participated in this matter will conduct the hearing. Such a hearing will determine

whether or not you should be 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,

Joanne L Rhoads M.D.

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

Enclosures:
21 CFR 312
21 CFR 16
Consent Agreement