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 LETTER (NIDPOE)

NOV - 6 1998

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

William H. Ziering, M.D.
4747 North First Street, Suite 177
Fresno, CA 93726

Dear Dr. Ziering:

Between April 12, 1995 and May 16, 1995, the Food and Drug Administration (FDA) inspected six of your clinical studies, which are identified below as "a" through "f"; and between October 7, 1998 and October 15, 1998, FDA investigated one of your clinical studies, which is identified below as "g". You are the investigator of record for the following seven studies:

a) Protocol [ ] "A Placebo-Controlled, Double-Blind Study of [ ] Aqueous Nasal Spray in Pediatric Patients with Spring Grass Seasonal Allergic Rhinitis" sponsored by [ ]

b) Protocol [ ] "A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Evaluation of the Safety, Efficacy and Effect on Asthma Quality of Life (AQL) of Salmeterol in Subjects Receiving Inhaled Corticosteroids" sponsored by Glaxo Pharmaceuticals.

c) Protocol [ ] "A Randomized, Double-Blind, Double-Dummy, Parallel Group, Comparative Trial of Inhaled, Fluticasone Propionate Rotadisks via Diskhaler 500mcg BID, Multi-Dose Powder Inhaler 500mcg BID, and Placebo in Adolescent and Adult Patients with Mild to Moderate Asthma" sponsored by Glaxo Research Institute.

d) Protocol [ ] "An Open-Label Study of Fluvastatin in the Treatment of Patients with Hypercholesterolemia in Clinical Practice Settings" sponsored by Sandoz Pharmaceuticals.

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e) Protocol [ ] "A Multicenter, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Safety and Efficacy of Oral Twice Daily Administration of [ ] in Patients with Mild to Moderate Asthma" sponsored by [ ]

f) Protocol [ ] "Randomized, Open-Label, Comparative Study of Rhinocort (budesonide) Nasal Inhaler versus Beconase (beclomethasone dipropionate) Inhalation Aerosol in the Treatment of Seasonal Allergic Rhinitis" sponsored by Astra USA.

g) Protocol [ ] "A Randomized, Double-Blind, Parallel-Group Trial To Assess The Topical Versus Systemic Efficacy of Fluticasone Propionate Rotadisks Via Diskhaler 500 MCG BID, 100 MCG BID, Fluticasone Propionate Tablets 20 MG QD, and Placebo in Adult Patients With Moderate Asthma" sponsored by Glaxo Pharmaceuticals.

The inspection and evaluation of the above studies is a part of 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 subjects have been protected.

Based on our evaluation of the information obtained by the Agency, the Center for Drug Evaluation and Research of FDA (Center) believes that you have 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), Parts 50, 56, and 312 (copy enclosed) and repeatedly or deliberately submitted false information.

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. In summary:

I. You submitted false information to the sponsor and FDA in required reports [21 CFR 312.70(a)].

A. For Glaxo study [ ]

1. Subject [ ]
The protocol required a pre-reversal pulmonary function test (PFT), with a percent predicted FEV_1 between [ ] for a prospective subject to qualify to enter this study. A post-

reversal PFT report was deliberately modified (i.e., "pre" was hand written on the trial [ ] PFT record, and the post-reversal time of 09:44 was crossed out and changed to the pre-reversal time of 09:07) to appear as if it were a pre-reversal PFT to qualify subject [ ] for this study.

2. Subject [ ]
The protocol required a blood specimen for an a.m. plasma cortisol determination be drawn between 07:00 and 10:00. Records (i.e., the white copy of the laboratory requisition that you sent to [ ] and the laboratory report from [ ] document that this specimen was drawn at 13:00. On October 15, 1998, you provided FDA with your copy of the laboratory requisition, on which you changed the collection time to falsely report that this specimen was collected at 08:00.

B. For Glaxo study [ ]

1. Subject [ ] The protocol excluded subjects with chronic obstructive pulmonary disease (COPD). The Screening Visit CRF reports that this subject did not suffer from COPD, but the subject's chart records document a history of COPD.

2. Subject [ ] - The protocol, in section 3.2-2, excludes subjects with diabetes. The Screening Visit CRF for this subject reports no medical conditions covered by section 3.2-2 of the protocol, but the subject's medical records document a history of diabetes since the age of 4. The CRF for this patient also fails to report insulin as a concomitant medication, although your office records specify that this subject was prescribed insulin.

II. You failed to maintain adequate and accurate case histories [21 CFR 312.62(b)].

A. For Glaxo study [ ]

1. Subject [ ] - The dates and times on the three required pre-dosing PFTs were changed from 10/24/94 to 10/25/94 and from 20:27 to 08:30, respectively. One post-dosing PFT had the date changed from 10/24/94 to 10/25/94 and the time changed from 21:03 to 09:00. Two other post-dosing PFTs, which were dated 10/25/94, had the times changed from 09:10 to 09:00. All these changes were made without any explanation of when the changes were made, who made the changes, or why the changes were made.

2. Subject[ ]- This subject was identified on all the PFT records, except the Week Four PFT records, as 63 years old, 184 lb, 72 inches tall, and male. On the Week Four PFT records, this subject was originally identified as 49 years old, 112 lb, 60 inches tall, and female. The gender alone was changed to male on 1/18/95 (i.e., the date of this change was noted on the PFT report), more than a month after the PFT tests were conducted.

3. Subject[ ]- The two pre-dosing and the three post-dosing PFTs were all reported as conducted on 10/31/94, at 09:34. The records do not document the required thirty minute interval between the pre- and post-dosing determinations(see protocol section 4.1-6).

4. Subject[ ]- The times on the three pre-dosing PFT records for 11/7/94 were changed from 06:35 to 08:00. The post-dosing PFT records were dated 11/7/94 and timed 08:30. The changes on the pre-dosing PFT records appear to have been made to comply with the protocol requirements and were made without any explanation of why or when the changes were made, or who made the changes.

B. For Glaxo study[ ]

The protocol requires all PFT tests, for all visits, to be conducted between 07:00 and 10:00 (see protocol section 4.0). However, the date, time, demographics, and sequence of PFTs were not accurately documented by the spirometer generated records as evidenced by extensive undocumented changes made to PFT data. For example:

1. Subject[ ]- The time was changed from 12:43 to 08:43 on the three PFT records for 6/24/94 (Visit Three).

2. Subject[ ]- The date on the three Visit Five PFT records was changed from 8/22/94 to 8/23/94 and the time on one of the three PFT records was changed from 20:08 to 07:00.

3. Subject[ ]- The times were changed on the PFT records for Visit One as follows: the times on the three pre-dosing PFTs were changed from 02:49 to 07:00; the times on two of the post-dosing PFTs were changed from 03:14 to 08:15 and from 03:20 to 07:00; while the time on the third post-dosing PFT was left as 03:20. The dates were changed on the three Visit Three PFTs from 8/10/94 to 8/11/94 and the times were changed from 19:04 to 07:00. The three Visit Four PFTs were conducted at 06:16, which was 44 minutes before the time period specified by the protocol. The three Visit Seven PFTs were conducted at 06:34, which was 26

minutes before the time period specified by the protocol. The time on the two Visit Nine PFTs, which were conducted on 10/13/94, were changed from 03:32 to 06:32 and one PFT reported as being done at 03:27 was changed to 06:32; the change to 06:32 was 28 minutes before the time specified by the protocol. The times on the three Visit Ten PFTs were changed from 20:19 to 07:00.

4. Subject [ ] For Visit One on 7/28/94, the times on the two pre-dosing PFT records indicate that these tests were conducted at 08:08, and the times on the two post-dosing PFTs indicate these tests were conducted at 08:42. One of the PFTs, on which the label had been changed from "Pre" to "Post", had the time changed from 08:08 to 08:42.

C. For [ ] study.

1. Subject [ ]- There are three PFTs available for Visit Four. Two of these PFTs indicate the subject was 18 years old, male, and weighed 150 lbs., which matches the description of this subject. The third PFT indicates the subject was 11 years old, male, and weighed 81 lbs.

2. Subject [ ] For Visit One, the two pre-albuterol challenge PFTs indicate this subject was 33 years old, 175 pounds, and male, which matches the description of the subject. The post-dosing PFTs indicate the subject was 49 years old, 146 pounds, and female.

D. Numerous signatures appearing throughout study records including signatures on several of the 1572's, subject consent forms, and CRF's, were submitted and represented as your authentic signature. During the inspection, and in your letter of July 11, 1995, you admitted that these signatures were made by others and not by you.

III. You failed to ensure that an investigation was conducted according to the investigational plan [21 CFR 312.60]

A. For Glaxo study [ ]

The protocol required a chest x-ray be taken at Visit One, unless a negative x-ray was done within 12 months prior to entry into the study.

1. Subjects [ ] For these subjects there is no documentation that either an x-ray was taken at Visit One or that a prior negative x-ray existed within 12 months.

2. Subjects [redacted] The records of these subjects indicate that chest x-rays were not taken prior to or at the screening visit, but were taken after the screening visit.

The protocol requires all PFT tests, for all visits, to be conducted between 07:00 and 10:00 (see protocol section 4.0). However, PFT tests were performed outside of this time frame. For example:

1. Subject [redacted] - For 5/26/94, the post-dosing PFT was conducted at 10:26. Moreover, the reversibility test consists of a pre-dosing PFT followed by a PFT performed 15 minutes after dosing (see protocol section 4.02(c)). For subject [redacted], the post-dosing PFTs were conducted approximately two hours after the reported pre-dose test and outside of the time frame specified by the protocol.

B. For Glaxo study [redacted]

Subject [redacted] - The protocol required a 30 minute interval between the pre-dosing and post-dosing PFTs. There are six PFTs dated 8/19/94, three pre-dosing and three post-dosing. Two of the three pre-dosing PFTs are stamped as conducted at 09:07. The three post-dosing PFTs are all stamped 09:19.

C. For [redacted] study [redacted]

1. Subject [redacted] - For Visit One, the protocol required a chest x-ray be taken unless an x-ray had been taken within the preceding twelve months. For Visit Five, the protocol required a blood sample be drawn and an ECG be performed. No records were available during the inspection to document the following: (1) that a chest x-ray was taken at Visit One or within the preceding twelve months; (2) that a blood sample for laboratory testing was drawn at Visit Five; or (3) that a pre-dose ECG was performed at Visit Five.

2. Subjects [redacted] - No chest x-ray was documented as taken at Visit One or within the preceding twelve months as required by the protocol.

IV. You failed to personally conduct or supervise the investigations [312.60] and [312.53 (c)(1)(vi)(c)]

By your own admission during the inspection and by letter of July 11, 1995, you acknowledged that portions of the studies reportedly conducted by you were in fact not personally conducted or supervised by you. Lack of proper conduct and supervision is documented by the following:

A. For[ ]study[ ].

You voluntarily informed[ ]the sponsor's CRO, on March 15, 1995 that the data generated by you was unreliable and should not be submitted to any regulatory agency.

B. For[ ]study[ ]

In a memo dated July 12,1995 you informed[ ]that "all subjects involved in this study were seen by me". However during an interview with FDA inspectors you retracted the statement that you personally saw all of the patients for "physical examinations, interpretation of skin tests, review of history at screening visit, fungal examinations, global assessment".

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 alleges that you have repeatedly and/or deliberately failed to comply with the cited regulations or repeatedly or deliberately submitted false information, and the Center 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, 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:

David A. Lepay, M.D., Ph.D.
Director
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
7520 Standish Place
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 you may be accompanied by a representative of your choosing. 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 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 the FDA.

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,

David A. Lepay, M.D., Ph.D.
Director
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research