DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

AUG 16 1999

CERTIFIED MAIL - RESTRICTED DELIVERY
RETURN RECEIPT REQUESTED

[ ]

NOTICE OF OPPORTUNITY FOR HEARING

Dear Mr. [ ]

The Center for Drug Evaluation and Research (the Center) of the United States Food and Drug Administration (FDA) has information indicating that your client, William H. Ziering, M.D., repeatedly and/or deliberately violated federal regulations in his capacity as an investigator in clinical trials with investigational new drugs. Additionally, the Center has information indicating that Dr. Ziering submitted false information to the sponsors of the clinical trials. These violations provide the basis for withdrawal of Dr. Ziering's eligibility to receive investigational new drugs as a clinical investigator.

The Center's findings are based on information obtained during the agency's inspections of Dr. Ziering's conduct as the investigator of record for the following 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;

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; and

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.

Pursuant to Title 21, Code of Federal Regulations (CFR), Part 312.70, the Center informed Dr. Ziering, by letter dated November 6, 1998, of the specific matters complained of and offered him an opportunity to respond in writing or in an informal conference. That same letter gave Dr. Ziering the option of entering into a consent agreement with the agency, thereby terminating any administrative proceeding against him.

In a letter dated December 4, 1998, you responded on Dr. Ziering's behalf and stated that Dr. Ziering did not desire to respond either in writing or in an informal conference. Instead, you and your client requested a hearing pursuant to 21 CFR 16.

Accordingly, Dr. Ziering is being offered an opportunity for a regulatory hearing pursuant to 21 CFR Parts 16 and 312, on the question of whether he is entitled to receive investigational new drugs. As you are aware, Dr. Ziering has the right to be advised and represented by counsel at all times. Any regulatory hearing on this matter will be governed by the regulations in 21 CFR 16 and the agency's guidelines on electronic media coverage of administrative proceedings, 21 CFR 10, Subpart C. A listing of the specific violations follows. These are the

matters that will be considered at the regulatory hearing. Applicable provisions of the CFR are cited for each violation.

I. Dr. Ziering submitted false information to the sponsor and FDA in required reports in violation of 21 CFR 312.70, and he failed to conduct his investigations according to the signed investigator statement, investigational plan, and applicable regulations in violation of 21 CFR 312.60.

A. Glaxo study [ ]

1. Subject 3713-T392 -- The protocol's inclusion criteria required that subjects have a pre-reversal pulmonary function test (PFT), with a percent predicted Forced Expiratory Volume (FEV_1) between [ ] A post-reversal PFT report was deliberately modified to appear as if it were a pre-reversal PFT to qualify subject 3713-T392 for this study.

2. Subject 3713-T392 -- The protocol required that the investigators draw a blood specimen for a morning plasma cortisol determination between 07:00 and 10:00. Records document that this specimen was drawn at 13:00. Records from Dr. Ziering, however, demonstrate that he changed the collection time to falsely report that this specimen was collected at 08:00.

B. Glaxo study [ ]

1. Subject 0665 -- The protocol excluded subjects with chronic obstructive pulmonary disease (COPD). Although the screening visit Case Report Form (CRF) for this subject indicates that the subject did not suffer from COPD, the subject's medical records clearly document a history of COPD.

2. Subject 0667 -- Section 3.2-2 of the protocol excluded subjects with diabetes. Although the screening visit CRF for this subject reports no medical conditions covered by section 3.2-2 of the protocol, the subject's medical records clearly document a history of diabetes since the age of four. The CRF for this subject also fails to document insulin as a concomitant medication, although Dr. Ziering's office records specify that this subject was prescribed insulin.

II. Dr. Ziering failed to maintain adequate and accurate case histories in violation of 21 CFR 312.62(b).

A. Glaxo study [redacted]

1. Subject 0664 -- The dates on the three required pre-dosing PFTs for this subject were changed from 10/24/94 to 10/25/94, and the times were changed from 20:27 to 08:30. The date on post-dosing PFT was changed from 10/24/94 to 10/25/94 and the time was changed from 21:03 to 09:00. The times on two other post-dosing PFTs, dated 10/25/94, were changed from 09:10 to 09:00. There is no explanation of when, why, or by whom these changes were made.

2. Subject 0665 -- This subject was identified on all the PFT records, except the Week Four PFT records, as 63 years old, 184 pounds, 72 inches tall, and male. On the Week Four PFT records, this subject was originally identified as 49 years old, 112 pounds, 60 inches tall, and female. The gender alone was changed to male on 1/18/95, more than a month after the PFT tests were conducted.

3. Subject 0671 -- 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, as required by section 4.1-6 of the protocol.

4. Subject 0674 -- 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 at 08:30. The changes on the pre-dosing PFT records appear to have been made to comply with the protocol requirements, and there is no explanation of why, when, or by whom changes were made.

B. Glaxo study [redacted]

Section 4.0 of the protocol required that all PFT tests for all visits be conducted between 07:00 and 10:00. 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 01303 -- The times were changed from 12:43 to 08:43 on the three PFT records from Visit Three on 6/24/94.

2. Subject 01308 -- The dates were changed from 8/22/94 to 8/23/94 on the three PFT records from Visit Five, and the time on one of the three PFT records was changed from 20:08 to 07:00.

3. Subject 01311 -- 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 PFTs records from Visit Three from 8/10/94 to 8/11/94 and the times were changed from 19:04 to 07:00. The three PFTs for Visit Four were conducted at 06:16, which was 44 minutes before the time period specified by the protocol. The three PFTs for Visit Seven were conducted at 06:34, which was 26 minutes before the time period specified by the protocol. The time on the two PFTs for Visit Nine, which were conducted on 10/13/94, were changed from 03:32 to 06:32. 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 PFTs for Visit Ten were changed from 20:19 to 07:00.

4. Subject 01316 -- 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. [ ]study [ ]

1. Subject 90099 -- There are three PFTs available for Visit Four. Two of these PFTs indicate the subject was 18 years old, male, and weighed 150 pounds, which matches the description of this subject. The third PFT indicates the subject was 11 years old, male, and weighed 81 pounds.

2. Subject 90101 -- 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 year old, 146 pounds, and female.

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

III. Dr. Ziering failed to ensure that an investigation was conducted according to the investigational plan, in violation of 21 CFR 312.60.

A. Glaxo study [ ]

1. The protocol required that 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.

a. Subjects 01301, 01302, 01304, and 01306 -- 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.

b. Subjects 01303, 01305, 01310, 01312, 01313, 01316, 01319, 01271, and 01273 -- The required chest x-rays were not taken prior to or at the screening visit, but were taken after the screening visit.

2. Section 4.0 of the protocol required that all PFT tests, for all visits, be conducted between 07:00 and 10:00 and section 4.02(c) requires that reversibility tests following the PFT be performed fifteen minutes after dosing.

Subject 01303 -- On 5/26/94, the post-dosing PFT was conducted at 10:26. 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. Glaxo study [ ]

Subject 0661 -- The protocol required a thirty-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. [ ] study [ ]

The protocol required that during Visit One a chest x-ray be taken unless an x-ray had been taken within the preceding twelve months, and at Visit Five a blood sample be drawn and an ECG be performed.

1. Subject 90089 -- 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 90098 and 90099 -- There was no documentation that a chest x-ray was taken at Visit One or within the preceding twelve months.

IV. Dr. Ziering failed to personally conduct or supervise the investigations in violation of 21 CFR 312.60 and 312.53(c)(1)(vi)(c).

A. [ ] study [ ]

In a memo dated January 12, 1995, Dr. Ziering informed [ ] that "all subjects involved in this study project were seen by me....". However, FDA's investigation of Dr. Ziering revealed that he did not personally see all of the subjects for "physical examinations, interpretation of skin tests, review of history at screening visit, fungal examinations global assessment."

B. [ ] study [ ]

On March 15, 1995, Dr. Ziering voluntarily informed [ ] the sponsor's contract research organization, that the data generated by him were unreliable and should not be submitted to any regulatory agency.

Dr. Ziering's request for a hearing must be made, in writing, within ten (10) business days of receipt of this letter and should be directed to:

Dr. James F. McCormack, Coordinator
Bioresearch Monitoring Program
Office of Enforcement
Division of Compliance Policy (HFC-230)
5600 Fishers Lane
Rockville, Maryland 20857
Telephone (301)827-0425
FAX (301)827-0482.

If no response to this letter is received by that time, Dr. Ziering will be deemed to have waived any right to a regulatory hearing, and a decision in this matter will be made based on the facts available to the agency. No hearing will be held.

A request for a hearing may not rest upon mere allegations or denials but must present specific facts showing that there is a genuine and substantial issue of fact that warrants a hearing. Pursuant to 21 CFR 16.26, a request for a hearing may be denied, in whole or in part, if the Commissioner or his delegate determines that no genuine and substantial issue of fact had been raised by the material submitted. A hearing will not be granted on issues of policy or law. Written notice of a determination of summary judgment will be provided explaining the reasons for denial of the hearing.

If Dr. Ziering wishes to respond but does not desire a hearing, he should contact Dr. McCormack within the time period specified above and submit a written response containing his reply. The response should state that Dr. Ziering waives his right to a hearing and that he wants a decision on the matter to be based on his written response and other information available to the agency.

The agency's offer to enter into a consent agreement, attached to the Notice of Initiation of Disqualification Proceedings and Opportunity to Explain dated November 6, 1998, remains available. Entering into a consent agreement would terminate the administrative procedures, but would not preclude the possibility of a corollary judicial proceeding.

No final decision by FDA has been made at this time on Dr. Ziering's eligibility to continue to use investigational new drugs. Moreover, there will be no prejudgment of this matter if Dr. Ziering declines to enter into a consent agreement and

decides instead to either request a regulatory hearing or to request that the decision be based on information currently available to the agency.

Sincerely,

Dennis E. Baker
Associate Commissioner
for Regulatory Affairs

Enclosures:
21 CFR Part 10, Subpart C
21 CFR Part 16
21 CFR Part 312.70