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 17 2004

Gary A. Cohen, M.D.
Allergy and Asthma Prevention Center
9855 Erma Road, Suite 105
San Diego, California 92131

Dear Dr. Cohen:

Between June 1 and June 22, 2000, Ms. Patricia A. Cochran, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of the following clinical studies in which you participated as the clinical investigator:

Protocol [ ] entitled: "Placebo-Controlled Dose Efficacy and Safety Study of [ ] in the Treatment of Asthma in Children Previously Maintained on Beclomethasone Dipropionate (Vanceril® 84 mcg Double Strength)," sponsored by [ ]

Protocol [ ] entitled: "One-Year, Open-Label Safety Study of [ ] and Beclomethasone Dipropionate (Vanceril® 84 mcg Double Strength) in Children with Asthma Previously Maintained on Inhaled Corticosteroids," and

Protocol [ ] entitled: "Long Term Safety Study of [ ] Metered Dose Inhaler and Beclomethasone Dipropionate (Vanceril® 84 mcg Double Strength) in the Treatment of Asthma in Subjects Previously Maintained on Inhaled Corticosteroids," sponsored by [ ]

Protocol [ ] entitled: "A Randomized, Double-Blind, Parallel Group Comparison Study of Inhaled Fluticasone Propionate (88mcg BID) Versus Montelukast Sodium (10mg QD), in Subjects Currently Receiving Beta Agonists Alone," and

Protocol [ ] entitled: "A Randomized, Double-Blind, Double Dummy, Parallel Group Comparison of [ ] with Oral Montelukast (10mg QD) in Subjects with Persistent Asthma Symptomatic on Concomitant Inhaled Corticosteroid Therapy," sponsored by [ ]

This inspection is 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.

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. In summary:

1. You failed to adequately supervise the clinical investigations [21 CFR 312.60].

When you signed the Statement of Investigator, Form FDA 1572, you agreed to take responsibility for the conduct of the clinical investigation at your site. You specifically agreed to personally conduct the clinical trials or to supervise those aspects of the trials you did not personally conduct. As the clinical investigator of the studies, you may delegate study tasks to qualified personnel under your direct supervision. You may not delegate your general responsibilities.

a. You inappropriately delegated study tasks to individuals not qualified to perform the delegated tasks.

For [ ]protocol[ ]you permitted an individual with no medical training (your office manager, Ms.[ ]to perform protocol-required assessments of the relationship between adverse events (AEs) and the study medication. We note that in a letter dated June 17, 1999, Ms.[ ]Senior Clinical Research Scientist, notified you to remedy issues she discussed with you and Ms. [ ]during a close-out monitoring visit (June 2-4, 1999). Ms.[ ]emphasized that you were required to assess the relationship of study medication to the AEs listed on the case report forms (CRFs) for subjects 1998 and 2000. She specifically noted that you should not have allowed the medically unqualified Ms.[ ]to perform this task.

b. You failed to adequately supervise those aspects of the clinical studies that you did not personally conduct.

Your lack of personal involvement and your failure to adequately supervise your staff resulted in, or contributed to, submission of false information to FDA or the sponsor (see item 2), failure to adhere to study protocols (see item 3), failure to prepare and maintain adequate and accurate study records (see item 4), failure to maintain adequate records of the disposition of the study drug (see item 5), and failure to assure IRB review of all pertinent components of the study (see item 6).

You had specific and repeated notice in letters, addressed to you, from the sponsor and study monitor for Protocol[ ]and the sponsors for Protocols[ ]and [ ]concerning protocol violations, discrepancies between source documents and CRFs, missing medical records, and discrepancies in drug accountability records:

- In a letter dated July 30, 1998, the study monitor expressed concern about the lack of substantiating medical records for any subject in Protocol[ ]
- In a letter dated August 18, 1998,[ ]staff[ ] noted during their monitoring visit (August 11-13, 1998) the lack of medical records for the majority of the subjects in Protocols[ ]and[ ]
- In a letter dated June 17, 1999, referenced in item 1.a. above, Ms.[ ]noted numerous drug accountability discrepancies for the majority of the subjects in Protocol [ ]She also noted that there were several errors "in the data contained in the source documents and the transcription to the CRFs," and that pages "in the CRFs ... were not completed although source data existed..." Ms.[ ]also noted that she and Ms.[ ]the[ ]monitor for Protocol[ ] told Ms.[ ]that[ ]concerns about study conduct were site issues, specifically that the work done by the study coordinators, Ms.[ ] and Mr.[ ]was "not of acceptable quality but that it appeared that neither of you were aware of this. We reminded[ ]that your signature on Form FDA 1572 indicates that you are ultimately responsible for the work done at the site under your direction."

Despite the feedback from the sponsors and/or study monitors over an 11-month period documenting an increased number and severity of regulatory violations, it appears that you did not institute corrective actions in response to these notifications. In fact, the violations noted during the FDA inspection in June 2000, and detailed below, confirm that you did not address these problems.

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

Protocols[ ]and[ ]required that a chest x-ray be obtained at visit 1 (if not obtained within the previous year). For the subject to meet Inclusion/Exclusion criteria for each of the studies, his/her x-rays had to be without clinically significant abnormalities. To document fulfillment of the chest x-ray requirement, you submitted reports for chest x-rays that appear to be falsified. Specifically:

Protocol[ ]

Based on documents dated 15 July 1998, 15 July 1998, 3 July 1998, and 3 July 1998, the chest x-ray reports for subjects A16/276, A15/277, A10/279, and A09/280, respectively, appear to be falsified. The heading of the chest x-ray reports for these subjects indicated that the chest

x-rays were performed at[ ] The names, dates, subject identifiers, and names of the referring physician in these chest x-ray reports differ in appearance (e.g., font) from chest x-ray reports authenticated by[ ](e.g., authentic chest x-ray report dated 5 June 1998). FDA has verified that the chest x-ray reports submitted for the four protocol subjects are not reports of chest x-rays performed on these subjects at[ ]

Protocol[ ]

Based on documents dated July 7, 1998 and July 10, 1998, the chest x-ray reports for subjects A08/137 and A09/135, respectively, appear to be falsified. The heading of the chest x-ray reports for these subjects indicated that the chest x-rays were performed at[ ]The names, dates, subject identifiers, and names of the referring physician in these chest x-ray reports differ in appearance (e.g., font) from chest x-ray reports authenticated by[ ](e.g., authentic chest x-ray report dated 5 June 1998). FDA has verified that the chest x-ray reports submitted for the two protocol subjects are not reports of chest x-rays performed on these subjects at[ ]

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

   a. Protocols[ ]and[ ]required that pulmonary function tests be performed at every subject visit. Part of the test consisted of a calculation of FEV_1 value. Subjects who demonstrated a[ ]or greater decrease in FEV_1 from the baseline value "must be discontinued" from Protocol[ ]and "may need to be discontinued" from Protocol[ ]the CRFs for both protocols instructed that the sponsor was to be notified if there was a[ ]or more decrease in the subject's FEV_1. Failure to determine percent-change from baseline in FEV_1 potentially placed subjects at risk by failing to identify subjects who were not adequately maintained on the study medication.

      1. Review of the CRFs indicates that you failed to calculate percent-change in FEV_1 from baseline at every visit for seven subjects in Protocol[ ](A13/274, A06/033, A01/039, A05/036, A03/034, A14/275, and A12/278).

      2. Review of the CRFs indicates that you failed to calculate percent-change in FEV_1 from baseline at every visit for two subjects in Protocol[ ](A02/321 and A08/325).

   b. Protocol[ ]required that Proventil use be monitored closely to determine whether subjects were overusing the drug (overuse defined by protocol as >[ ] Overuse could be grounds for discontinuing subjects from the study since overuse is associated with increased mortality and may be an indication that more aggressive medical intervention is necessary. The CRF for subject A02/321 failed to indicate the amount of Proventil use between Visits 3 and 4.

   c. Protocol[ ]inclusion criteria required a baseline plasma cortisol level of[ ]Subject A14/122 was enrolled despite a baseline plasma cortisol level of[ ]

d. Protocol[ ]required that baseline plasma cortisol levels for the time-sensitive [ ]Test be obtained between 8:00 a.m. and 9:00 a.m. For subject A13/133, the baseline level was obtained at 10:35 a.m., thereby invalidating the test results.

e. Protocol[ ]required that each subject's diary card document Ventolin® use on at least 6 of the 7 days preceding visit 2, and that the daily symptom score be[ ]for any listed asthma symptom category on 4 or more of the 7 days prior to visit 2. The following subjects did not meet these criteria and should not have been enrolled:

1. Subjects 39631, 39634, 39635, 39639, 39640, 39641 and 39643 used Ventolin® on 5, 4, 0, 5, 4, 4 and 5 days, respectively, during the 7 days preceding visit 2.

2. Subjects 39633 and 39634 had daily symptom scores[ ]on only 1 of the 7 days prior to visit 2.

f. For Protocol[ ]certain treatment visits were outside the protocol-specified time frames for the following subjects:

Subject	Treatment #	Due Date	Actual Date
1991	51	2/6/99	2/8/99
1993	49	2/6/99	2/8/99
1998	56	2/23/99	2/25/99

4. You failed to prepare and maintain adequate and accurate records [21 CFR 312.62(b)].

You failed to prepare and maintain source documents that reflect data recorded in CRFs. For example:

a. In records for Protocol[ ]the following discrepancies between source documents and CRFs were noted:

Subject	Information in Source Document	Information in CRF
A02/138	Subject used Albuterol sulfate 180 µg inhaler PRN: 11/96 – 7/1/98	Usage not recorded
A16/131	Subject used Flunisolide 500 µg inhaler QD: 3/96 – 8/97	Usage not recorded
A09/135	Intraocular pressure both eyes: 18mmHg	Intraocular pressure both eyes: 16mm Hg
A13/133	FEV_1 values for visit 3 and 5: 1.44 and 1.47	FEV_1 values for visit 3 and 5: 1.48 and 1.50
A04/140	Proventil washout performed on 7/4/98	Proventil washout performed on 7/12/98

b. In records for Protocol[ ]the CRFs indicate that subjects A13/274 (visit 3 CRF) and A07/037 (visit 6 CRF) had used > 12 puffs/day or > 2 nebulized treatments/day of

Proventil for 2 consecutive days since the previous visit. The source documents reflect instead that the subjects did not use any puffs or nebulized treatments during that timeframe.

c. In records for Protocol[ ] you failed to accurately report in the CRF the information that is contained in the source document for subject A04/323 at visit 9. On 7/20/98, the source document noted that 3 inhalers were dispensed. On 12/8/98, the number 3 was crossed out and replaced with a 6. However, the CRF was not changed to reflect that 6 inhalers were dispensed.

5. You failed to maintain adequate records of the disposition of the study drug [21 CFR 312.62(a)].

a. In Protocol[ ]the drug disposition records were inadequate in that they reflect the following discrepancies between the subjects' diaries and the drug logs as to drugs dispensed and returned, and thereby used by the subject:

Subject	Treatment #	Drug log # capsules dispensed	Diary # capsules used	Difference	Drug log # capsules returned	Discrepancy
39638	87	180	139	41	38	3
39636	86	36	25	11	12	1
39635	85	216	133	83	43	40
39633	83	216	146	70	57	13
39639	89	180	116	64	62	2

b. In Protocol[ ] the drug disposition records were inadequate in that they reflect the following discrepancies between the subjects' diaries and the drug logs as to drugs dispensed and returned, and thereby used by the subject:

Subject	Drug log # capsules dispensed	Diary # capsules used	Difference	Drug log # capsules returned	Discrepancy
1998	108	70	38	37	1
1992	108	87	21	21	0
1994	36	8	28	14	14
2000	72	55	17	14	3
1997	108	83	25	25	0
1999	72	56	16	24	8

c. In Protocol[ ]the drug disposition records were inadequate in that they reflect the following discrepancies between the subjects' diaries and the drug logs as to drugs dispensed and returned, and thereby used by the subject:

Subject	Drug log # inhaler doses dispensed	Diary # inhaler doses used	Difference	Drug log # inhaler doses returned	Discrepancy
1998	240	155	85	72	13
1992	180	190	10	86	76
1994	60	16	44	15	29
2000	120	111	9	51	42
1997	180	166	14	5	9
1999	120	9	9	17	8

6. You failed to assure IRB review [21 CFR 312.66].

You failed to obtain IRB approval for the complete informed consent form for Protocol [ ]in that you did not submit to the IRB the associated assent form, that was required to be signed by children participating in the study. A letter dated May 15, 1998, from your office to[ ]Institutional Review Board, states that the child's assent form was omitted when the consent was approved.

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, FDA asserts that you have submitted false information to FDA or the sponsor in a required report and that you repeatedly or deliberately failed to comply with the cited regulations for new drugs and it 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) 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 (HFD-45)
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
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 with you all pertinent documents, 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 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 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 Part 16 (enclosed) and 21 CFR 312.70 (enclosed). 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,

Joanne L Rhoads M.D.

Joanne L. Rhoads, M.D., MPH
Director
Division of Scientific Investigations, HFD-45
Office of Medical Policy
Center for Drug Evaluation and Research

Enclosures:
21 CFR 312
21 CFR 16
Consent Agreement