DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

WARNING LETTER

CERTIFIED MAIL - RESTRICTED DELIVERY
RETURN RECEIPT REQUESTED

JUN 11 2002

Leonard J. Caputo, M.D.
The Asthma and Allergy Institute
124 University Boulevard, Suite 2
Mobile, Alabama 36608

Ref: 02-HFD-45-0202

Dear Dr. Caputo:

Between August 29 and 31, 2000, Ms. Barbara D. Wright, representing the Food and Drug Administration (FDA), conducted an inspection of the following clinical studies in which you participated:

1. Protocol [redacted] titled, "A Multicenter, Double-blind, Placebo-controlled, Randomized, Parallel Trial Evaluating the Efficacy and Safety of [redacted] vs CFC Flunisolide in Pediatric Patients with Mild to Moderate Asthma." [redacted] sponsored the study and submitted the results to FDA in support of NDA [redacted]

2. Protocol [redacted] titled, "One-Year, Open-Label Safety Study of [redacted] Metered Dose Inhaler [redacted] and Beclomethasone Dipropionate (Vanceril® 84 mcg Double Strength) in Children with Asthma Previously Maintained on Inhaled Corticosteroids," performed for [redacted] under IND [redacted]

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 who participate in such studies are protected.

At the conclusion of the inspection Ms. Wright presented and discussed with you the items listed on the Form FDA 483, Inspectional Observations. We have reviewed the inspection report, the documents submitted with that report, and your letter to Mr. Michael Roosevelt, New Orleans District Office, dated October 5, 2000, in response to the items on the Form FDA 483, and we find your responses to be unacceptable.

Based on evaluation of the information obtained during the inspection, we have determined that you submitted false information to FDA or the sponsor in required reports and 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, Part 312 (21 CFR 312) (enclosure 1). Our investigation revealed that you did not fulfill your obligations as a clinical investigator.

This letter provides you with written notice of the matters under complaint. A listing of the violations follows. The applicable provisions of the CFR are cited for each violation.

1. **FAILURE TO ADEQUATELY SUPERVISE THE CLINICAL STUDY AS YOU COMMITTED TO DO WHEN YOU SIGNED THE FORM FDA 1572 (21 CFR 312.60)**

   Your failure to adequately supervise the study resulted in the submission of false information to FDA or the sponsor in required reports that are subject to Section 505 of the Federal Food, Drug, and Cosmetic Act.

2. **SUBMISSION OF FALSE INFORMATION TO THE SPONSOR [21 CFR 312.70(a)]**

   You submitted false information to the sponsor and FDA in that Pulmonary Function Test (PFT) results for three subjects were altered to include subjects that otherwise would have been excluded from the study. The following subjects did not meet the protocol-specified criterion of [redacted] in their Forced Expiratory Volume (FEV_1) on a Post-Medication PFT:

   a. Subject #2617 [redacted] Post-Medication value was changed from [redacted] to [redacted] and the "Per Cent Change" value was changed from [redacted] to [redacted]

   b. Subject #2614 [redacted] time of calibration on the pre-medication PFT report dated 2/15/99 was changed from "8:14:48 a.m." to "8:44:48 a.m." This pre-medication PFT report was misrepresented as a post-medication PFT report. The value obtained on this pre-medication PFT report ([redacted]) was entered as the Post-Bronchodilator FEV_1 value on the Case Report Form (CRF) dated 2/15/99. No authentic post-medication PFT report for subject #2614 [redacted] was available at your site for 2/15/99.

   c. The PFT report for subject #2609 [redacted] dated 12/17/98 was placed on top of the 12/3/98 report and obscured the machine generated date and time information of the 12/3/98 record. "Post" and "[redacted]" were handwritten in the margin next to the 12/3/98 report. The 12/3/98 PFT report was thus misrepresented as a post-medication PFT report. The value obtained on the 12/3/98 PFT report [redacted] was entered on the CRF dated 1/14/99 as the Post-Bronchodilator FEV_1 value and was alleged to have been obtained on 12/17/98. No authentic post-bronchodilator PFT report from 12/17/98 was available at your site.

3. **FAILURE TO CONDUCT THE CLINICAL STUDY IN ACCORDANCE WITH THE APPROVED PROTOCOL (21 CFR 312.60)**

   You failed to conduct the study in accordance with the approved protocol in that:

   a. Five subjects failed to meet the inclusion criterion of [redacted] in FEV_1 after albuterol treatment, as follows:

Subject #	Pre-Med. FEV_1	% of Predicted Value	Post-Med. FEV_1	% of Predicted Value	Change
2601					
2607					
2609			no record available	incalculable; Post-Med PFT unavailable	incalculable; Post-Med PFT unavailable
2614			no record available	incalculable; Post-Med PFT unavailable	incalculable; Post-Med PFT unavailable
2617					

Your letter dated October 5, 2000, states that your clinical coordinator obtained the sponsor's permission for enrollment of subjects #2601 and #2607. The PFT report for subject #2607 has a handwritten note in the margin, "Spoke to Enrollment OK." The note appears to be in the handwriting of the study coordinator, but is not signed or dated. There is no annotation in the file for subject #2601 of this exception. There was no documentation available to support sponsor exceptions for enrollment of subjects not meeting inclusion criteria.

b. Subject #2608 was enrolled in Protocol less than days after treatment with the investigational drug from Protocol in violation of Protocol Protocol Section 3.4.2.2. states that the "Washout time prior to screening visit" for investigational drugs is

Subject #2608 medical records state that on 5/7/99, subject "[c]ame into office for Protocol Study procedures completed...Subject advised of post study medication plan. "

Subject #2608 medical records state that on 6/3/99, subject "[c]ame into office for Protocol Study discussed, consent reviewed, subject and parent signed consent, copy given to subject. Study procedures & lab work completed. Instructions & diaries reviewed. Proventil dispensed. Will return in 2 weeks for next study visit. EKG & chest xray, eye exam scheduled. "

The elapsed time from 5/7/99 to 6/3/99 is 28 days.

4. FAILURE TO MAINTAIN ADEQUATE AND ACCURATE RECORDKEEPING AND CASE HISTORIES [21 CFR 312.62(b)]

You failed to maintain adequate and accurate case histories in that:

a. Discrepancies for vital signs were noted between the medical charts and what was recorded in the case report forms for 7 subjects [#2610 (visit 1), #2611 (visit 1), #2620 (visits 1 & 6), #2621 (visit 4), #2601 (visit 2), #2612 (visits 3, 5, & 6), and #2617 (visit 3)].

b. The original post-medication PFT report dated 3/17/99 was not available for subject #2620.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical studies of investigational drugs. It is your responsibility as the investigator of record to ensure adherence to FDA regulations. You must address these deficiencies and establish procedures to ensure that any on-going or future studies will be in compliance with the regulations.

Within fifteen (15) working days of receipt of this letter, you must notify this office in writing of the specific corrective actions you have taken or will be taking to address these deficiencies and to achieve compliance with the FDA regulations. If corrective actions cannot be completed within 15 working days, you may request an extension of time in which to respond by stating the reason for the delay and the time within which the corrections will be completed. We will review your response and determine whether the actions are adequate. Failure to correct the deficiencies may result in regulatory action without further notice.

If you do not wish to submit a corrective action plan, you may wish to consider entering into a consent agreement with the agency regarding your future use of investigational new drugs. (enclosure 2). Entering into this consent agreement and abiding by it will satisfy your obligation to address the deficiencies noted above and will help you achieve and maintain compliance with the FDA regulations.

Your reply should be sent to:

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branches I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Food and Drug Administration
7520 Standish Place, Room 125
Rockville, Maryland 20855

Sincerely yours,

Joanne L Rhoads M.D.

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

Enclosures:
#1 - 21 CFR 312
#2 - Consent Agreement