DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

g1069d

Food and Drug Administration
Center for Biologics Evaluation and Researc
1401 Rockville Pike
Rockville MD 20852-1448

By Certified Mail - Return Receipt Requested

CBER - 01 - 019

APR - 4 2001

Warning Letter

William A. Shrader, Jr., M.D.
141 Paseo de Paralta, Suite A
Santa Fe, New Mexico 87501

Dear Dr. Shrader:

During an inspection that ended on November 15, 2000, Ms. Patricia Cortez, an investigator from the Food and Drug Administration (FDA), documented that you administered Enzyme Potentiated Desensitization (EPD) allergenic products to human subjects in violation of the Public Health Service Act (PHS Act) and the Federal Food, Drug, and Cosmetic Act (FD&C Act).

EPD allergenic products are biological products as defined in Section 351(i) of the PHS Act in that they are biological products applicable to the prevention, treatment, or cure of diseases or conditions of human beings, and are subject to Section 351(a) of the PHS Act. EPD allergenic products also are drugs within the meaning of Section 201(g) of the FD&C Act in that they are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man.

The inspection revealed the following violations.

1. Section 351(a) of the PHS Act is being violated in that unlicensed biological products (EPD allergenic products) are being introduced or delivered for introduction into interstate commerce with no approved biologics license application (BLA) in effect, nor any investigational new drug application (IND) in effect pursuant to Section 505(i) of the FD&C Act.

2. The EPD allergenic products used in your study are misbranded under Section 502(f)(1) of the FD&C Act because the labeling fails to bear adequate directions for use. Adequate directions cannot be written for unapproved drugs.

3. Under restrictions imposed by the FDA upon the Great Lakes College of Clinical Medicine (GLCCM) Institutional Review Board (IRB) on March 9, 2000, the GLCCM IRB instructed you to discontinue the enrollment of new subjects. Nevertheless, you continued to enroll new subjects.

4. The consent forms you have given to prospective study subjects since March 14 2000, are improper for the following reasons:

   A. The consent form contains four references to the FDA in your description of your study of EPD immunotherapy. Potential study subjects may misinterpret these statements since they imply that the FDA reviewed the research and permitted the research to be conducted, when, in fact, as indicated above in item 1, you did not even seek authorization to lawfully use EPD allergenic products in human subjects under the PHS Act and the FD&C Act.

   B. The consent form contains five references to GLCCM IRB, and implies that the study is conducted with the approval of the GLCCM IRB. As described above in item 3, the IRB suspended new enrollment of study subjects, and, therefore, the consent form does not represent the true status of the study.

   C The consent form contains exculpatory language through which the subject or the subject's representative is made to waive or appear to waive the subject's legal rights, in violation of the informed consent regulations found at Title 21, Code of Federal Regulations Part 50 (21 CFR § 50.20).

5. You charged the subjects money for the EPD allergenic products, which is prohibited by 21 CFR § 312.7(b).

These statutory and regulatory provisions exist to protect the rights, safety, and welfare of the human subjects of research and to assure the integrity of clinical research. Your failure to adhere to these important requirements is a serious violation.

6 Furthermore, as directed by the FDA, the GLCCM IRB terminated your study of EPD allergenic products, as described in the GLCCM IRB letter to you dated January 15, 2001. The GLCCM IRB instructed you to return a written acknowledgment to the GLCCM IRB that the study was terminated and that you notified all co-investigators of the termination. In your reply letter to the GLCCM IRB dated January 29, 2001, you state that "...the FDA was allowing us to continue EPD on patients already enrolled in the study; we have not heard otherwise." This statement is not correct. In our telephone conference with you and [redacted]., the manufacturer, on July 14, 2000, the FDA representatives advised you that the administration of EPD allergenic products outside the framework of the IND regulations is illegal. In addition, FDA representatives have discussed the requirements for an IND to study EPD, with

you and the manufacturer, yet no such application has been submitted. Your letter to the GLCCM IRB dated January 29, 2001, further states, "...I would only advise physicians to stop EPD if we were advised directly by Dr. Richman [FDA]."

This letter confirms the prior notice you have received that you and your co-investigators must discontinue administration of EPD allergenic products to human subjects. We will send a copy of this letter to all known co-investigators, as listed in the enclosure. As part of your response to this letter, you should provide this office with the names and addresses of any additional co-investigators. We consider a co-investigator to be any clinician who prescribed or administered EPD allergenic products in the United States since January 1, 1999.

This letter is not intended to be an all-inclusive list of deficiencies observed at your facility. It is your responsibility to ensure adherence to each requirement of the FD&C Act, PHS Act, and relevant regulations.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action being initiated by the FDA without further notice. These actions include, but are not limited to, seizure and/or injunction.

You should notify this office in writing within fifteen (15) business days of receipt of this letter of the specific steps you have taken to correct the noted violations. Corrective actions include, but are not limited to, immediately discontinuing administration of EPD allergenic products to human subjects, and immediately halting the shipment and receipt of EPD allergenic products. Please submit documentation of the corrective actions.

EPD allergenic products may only be studied in the United States if there is an IND in effect. You may submit an IND application to the FDA pursuant to 21 CFR Part 312. If an IND is submitted, no clinical investigation is permitted to proceed until the IND is in effect, as described in 21 CFR §§ 312.20 and 312.40. These regulations are available at http:www.access.gpo.gov/nara/cfr/index.html.

Your response to this letter should be sent to the following address:

Patricia Holobaugh (HFM-664)
Division of Inspections and Surveillance
Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448
Telephone (301) 827-6221

Sincerely,

Steven A. Masiello
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation
and Research

Enclosure

cc: [redacted]

Thomas Allison, Director
Food and Drug Administration
P.O. Box 25087
Denver, Colorado 80225-0087