



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Central Region *m2818m*

Food and Drug Administration
Waterview Corporate Center
10 Waterview Blvd., 3rd Floor
Parsippany, NJ 07054

Telephone (973) 526-6005

July 21, 1999

WARNING LETTER

Mr. John E. Nine
President, Technical Operations
Schering Laboratories
Schering-Plough Corporation
2015 Galloping Hill Road
Kenilworth, New Jersey 07033-0503 FILE NO: 99-NWJ-31

Dear Mr. Nine:

An inspection of your drug manufacturing facilities located in Union and Kenilworth, New Jersey, and conducted by Food and Drug Administration investigators between April 12 and May 28, 1999, found significant deviations from current Good Manufacturing Practice (cGMP) regulations for Finished Pharmaceuticals (Title 21, Code of Federal Regulations, Part 211). Such deviations cause finished pharmaceuticals to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (the Act).

Our investigation found the following deviations:

- 1) Failure to reject finished drug products that did not meet established test specifications. Specifically, Vanceril DS Inhalation Aerosol lots 8-DMT-625 and 8-DMT-626 initially failed the established [REDACTED] limits set for [REDACTED]. These batches were resampled and retested months later and were released.
- 2) Failure to follow written test procedures in that nine batches of Vanceril DS Inhaler initially failed the [REDACTED] limits established for the [REDACTED] of [REDACTED] and were not tested to [REDACTED] as required. Instead, these batches were resampled between two and one half months and four months after manufacture, retested, and released. These batches include 8-DMT-627, 8-DMT-628, 8-DMT-629, 8-DMT-630, 8-DMT-632, 8-DMT-635, 8-DMT-636, 8-DMT-637, and 8-DMT-638.

- 3) Failure to subject [REDACTED] of Proventil (albuterol) Inhalation Aerosol to the [REDACTED] test as required. The test was conducted on only one canister per tray.
- 4) The [REDACTED] unit used to conduct the [REDACTED] test was not qualified for this function.

The above is not intended to be an all-inclusive list of violations. As a manufacturer of finished pharmaceuticals, you are responsible for assuring that your overall operation and the products you manufacture and distribute are in compliance with the law.

Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these violations and to establish procedures to prevent their recurrence. Failure to promptly correct these violations may result in regulatory action without further notice, such as seizure and/or injunction.

We recognize that your firm had voluntarily ceased distribution of the Proventil Inhalation Aerosol in response to our investigators findings. We are also aware of the potentially serious threat to the public health that might have resulted from a market shortage of this product.

We acknowledge that on June 7, 1999 members of your organization arrived at the New Jersey District Office to discuss with us and representatives of the Center for Drug Evaluation and Research (CDER), via teleconference, the observations concerning the [REDACTED] testing of the Proventil Inhaler canisters and the Vancericil particle size deviations.

We are mindful of the meeting held at FDA Headquarters on June 17, 1999 between CDER and Schering representatives to discuss conditions under which your firm may resume shipment of the Proventil Inhalers. That meeting resulted in a June 25, 1999 letter from CDER officials to Dr. Alexander Giaquinto, Sr. Vice President, Worldwide Regulatory Affairs detailing a four-phase proposal for the release of batches of Proventil (albuterol) Inhalation Aerosol. The four-phase proposal outlines the interim steps to be taken by your firm in order to continue distribution of this product. This includes developing and validating a new in-process test for [REDACTED] testing on the canisters. This data must be submitted to the agency as a "Prior Approval" supplement. Your firm must strictly adhere to that proposal in order to continue distributing Proventil Inhalers.

Schering Laboratories
Kenilworth/Union, New Jersey

We are also in receipt of your firm's June 15, 1999 written response to the observations noted on the Inspectional Observations Form FDA-483. We have the following comments:

The response to FDA-483 points 1a and 1b is not satisfactory. As we pointed out in our previous Warning Letter of October 23, 1998, drug products failing to meet established standards or specifications and any other relevant quality control criteria shall be rejected. Retesting later is not an acceptable practice. The approved [REDACTED] specification of [REDACTED] with [REDACTED] testing for Vanceril DS Inhalation Aerosol must be adhered to until such time as a supplement to the appropriate NDA is filed and approval is received from agency officials.

The response to FDA-483 point 3 concerns the reduction in the [REDACTED] testing for the Proventil Inhalers. This issue was discussed with members of your firm at the previously mentioned June 17, 1999 meeting with CDER representatives. The four-phase proposal was presented by the Agency in the June 25, 1999 letter and requires your firm to develop and validate a new in-process test for [REDACTED] testing on the canisters. This data is to be submitted to the agency as a "Prior Approval" supplement.

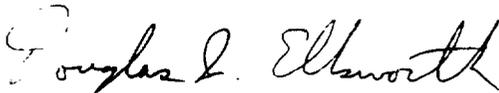
The corrective actions to FDA-483 points 2, 4 and 5 through 12 will be confirmed at a future inspection.

The response to FDA-483 points 13 through 16 concerning Adverse Drug Experience Reporting requires further review and will be commented on at a later date.

We request that you reply in writing within 15 working days of the steps you are taking to correct the violations. Upon receipt of your reply, if you still desire a meeting as indicated in your correspondence of July 6, 1999, we will make arrangements as to a convenient date and time.

Correspondence concerning this matter should be directed to the Food and Drug Administration, Attention Richard T. Trainor, Compliance Officer.

Sincerely yours,



DOUGLAS I. ELLSWORTH
District Director
New Jersey District

CERTIFIED MAIL
RETURN RECEIPT REQUESTED