



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Central Region *MJB/lor*

Telephone (973) 526-6005

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

October 23, 1998

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-02

Dear Mr. Nine:

An inspection of your drug manufacturing facilities located in Kenilworth and Union, New Jersey, and conducted by Food and Drug Administration investigators between June 29, 1998, and July 30, 1998, 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) There is no assurance that the written production and process control procedures established for coating the Claritin-D 12 Hour Repetabs are sufficient to produce a product that has the quality it is purported or represented to possess. The duration of each coating cycle is determined by the pan operators and is based on a visual determination that the coating solutions are evenly distributed before proceeding to the next step. It was noted that 78 of [REDACTED] batches made in 1997, and 79 of [REDACTED] batches made in 1998 were rejected due to in-process dissolution failures.
- 2) The partial release of various products even though there was no data to invalidate out-of-specification (OOS) results. Some examples include:
 - a) Claritin D 12 Hour Repetab lot #7-JRP-954 was only partially rejected due to a failing in-process dissolution rate of 76% from pan 4 at the third hour dissolution timepoint. Some 61 partial releases were noted for this product for the period 1997-1998.

- b) Diprolene Ointment 0.05%, batch #6-HYA-2 was only partially rejected after obtaining OOS assay results of 111.8% and retest results of 116.0%, and 149.0%.
 - c) Proventil Inhaler 90mcg 17 g. cans, batch #6-BBS-821 was only partially rejected following failing pressure results ranging from 42 to 49 psi. Retest results confirmed failing results ranging from 43 to 53 psi.
 - d) Nasonex Nasal Spray 50mcg 17g, batch #8KTL-518 and Nasonex Nasal Spray 50mcg 10g, batch #8KTL-531 were only partially rejected after failing to conform to Uniformity of Spray Content specifications during final product release testing.
- 3) The mingling and subsequent packaging of one pallet of semi-finished bottles of rejected Nasonex Nasal Spray batch 7-KTL-1 with Nasonex Nasal Spray batch 7-KTL-6, which was subsequently released in part.
 - 4) There is no data to support the [REDACTED] hour time period established to fill Proventil Aerosol Inhaler 90 mcg. 17 g. cans. It was noted that batch #7-BBS-570 was filled in excess of [REDACTED] hours; out-of-specification results were confirmed for non-volatile matter and the batch was partially released.

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 acknowledge that you have submitted to this office a response concerning our investigator's observations noted on the Inspectional Observations Form FDA-483. We have the following comments:

Your response to FDA-483 points 1 and 16 (Warning Letter item 1, inclusive) and FDA-483 point 2, indicates that a task force of representatives from Research, Quality Control and Manufacturing Operations was commissioned to further evaluate the critical manufacturing parameters of Claritin-D 12 Hour Repetabs and Proventil Repetabs. It is requested that a timetable be provided as to when this evaluation will be accomplished. Your response to FDA-483 point 1 also indicates you plan to return to a [REDACTED] pan coating operation for Claritin-D 12 Hour Repetabs. This would appear to resolve the issue of partial releases based on the release criteria for this product (Warning Letter item 2a), but does not resolve the reasons for the in-process dissolution failures. While we

Schering Laboratories
Kenilworth/Union, New Jersey

acknowledge that a supplement was submitted to relax the in-process ~~XXXXXX~~ dissolution specification, pending approval, the current in-process specifications are considered valid and must be followed.

Your responses to FDA-483 points 6, 9, 11 (Warning Letter items 2b, c, d, respectively), FDA-483 points 7 and 8 (Warning Letter items 3 and 4, respectively) and FDA-483 point 3B do not adequately address the issue of partial releases. Released products are expected to conform to established specifications from the beginning to the end of production. Current regulations specify that drug products failing to meet established standards or specifications and any other relevant quality control criteria shall be rejected. Reprocessing may be performed, provided certain criteria are met according to written procedures. The practice of partial releases, no matter how stringent the re-sampling, raises doubt as to the safety and efficacy of the product being released. It is not acceptable to substitute testing over adequate control of a process.

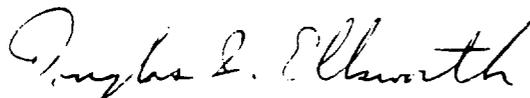
Your response to FDA-483 point 13 indicates that the moisture problem may be due to sample handling. The response is not clear as to how this conclusion was arrived at nor does it explain exactly what corrective actions have been implemented to provide for more controlled sample handling. Please advise us.

Your responses to FDA-483 points 3A, 4, 5, 10, 12, 14, and 15 appear adequate.

We request that you reply within 15 working days of the steps you are taking to correct the violations.

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