



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Central Region

M3829n

Telephone (973) 526-6008

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

WARNING LETTER

**Certified Mail
Return Receipt Requested**

File # 00-NWJ-36

June 9, 2000

Peter S. Jensen
President, Worldwide Supply Organization
SmithKline Beecham Pharmaceuticals
1 Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101

Dear Mr. Jensen:

We conducted an inspection of your manufacturing facility, located at 101 Possumtown Road, Piscataway, New Jersey, from April 5 to April 27, 2000, and found significant violations of the regulations covering Current Good Manufacturing Practices for Finished Pharmaceuticals (Title 21, Code of Federal Regulations, Parts 210 and 211). These violations cause your drug products, Timentin 3.1 g/50 cc vials and Ticarcillin 3 g/50 cc vials, to be adulterated under Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (the Act). The violations include:

1. Your quality unit released for distribution batches of drug products that failed to meet established specifications [21 CFR 211.22 and 211.165(f)].
 - a. Your quality unit released batches NW3585, NW3539, RB3603 and NW3588 of Timentin 3.1 g/50 cc vials that failed to meet content uniformity specifications. The quality unit, based on limited additional testing, concluded that the content uniformity problems were an end-of-fill phenomenon and released portions of the batches believed to be unaffected by these problems. However, the testing used to reach this conclusion was inadequate in that it did not determine the cause of the failures and the exact point that the failures began to occur. Moreover, the additional testing and the conclusions drawn from that testing are inconsistent with USP testing procedures and your firm's processing procedures established to account for end-of-fill problems.
 - b. Your quality unit released batch 48649DA of Ticarcillin 3 g/50 cc vials that failed specifications for the presence of particulates. The quality unit concluded that the

particulates were present only in the end-of-fill portion of the batch and released the portion of the batch believed to be unaffected by the presence of particulates. However, this conclusion is not supported by any investigation to show that foreign particles were only introduced at the end of the fill.

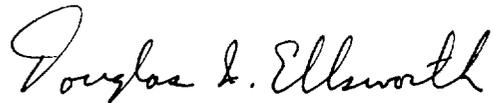
2. Your quality unit rejected initial out-of-specification results of finished product testing without conducting an adequate investigation [21 CFR 211.22, 211.192, and 211.194]. The inappropriate handling of out-of-specification results affected release decisions for Timentin lot NN3511 (content uniformity), lot 52650DA of Ticarcillin (white particulates), and lots NB3407, NB3408 and NC3424 of Timentin (white particulates). Upon obtaining an initial out-of-specification result for each lot, your quality unit collected additional samples and based its release decisions on the passing results obtained from the additional samples. The quality unit did not conduct an investigation to determine if production or laboratory problems could have caused the original failing results. Moreover, your quality unit did not report the failing results. All results should be reported and considered in making final release decisions.
3. Your filling validation for Timentin 30:1/3.1 g blend was inadequate [21 CFR 211.100]. Your 1996 validation effort produced end-of-fill results that did not meet your acceptance criteria for label claim uniformity. Changes were then made to your process, but these changes were not re-validated to assure their effectiveness. Since your 1996 validation effort and changes to your process, you have experienced content uniformity failures for 11 lots. These failures suggest that your corrective actions may not have been adequate and that your filling process needs to be revalidated.
4. Your firm failed to conduct media fills as required by your validation procedures for powder filling [21 CFR 211.100]. Your validation protocol requires specific media fill challenges yearly. Your firm did not conduct any two-hole stopper media fill in calendar year 1999. This specific media fill is intended to demonstrate the sterility of the [REDACTED] filling unit during aseptic filling.

This letter may not list all the deviations present at your manufacturing facility. As a manufacturer of drug products for human use, you are responsible for assuring that your manufacturing facility and the products produced at this facility are in compliance with the Act and Current Good Manufacturing Practice regulations. We routinely advise other Federal agencies about Warning Letters we issue addressing drug products so that the agencies may take this information into account when considering the awarding of contracts for the purchasing of products. Also, the FDA may not approve pending new drug applications or supplements to existing applications referencing your Piscataway, New Jersey manufacturing facility until you correct the violations listed above.

You should take prompt action to correct the violations listed above and to establish procedures to prevent further violations of the Act and applicable regulations. If you do not promptly correct these violations, the FDA may take further regulatory action, such as seizing your products or enjoining your facility from operating.

Please respond in writing within 15 days from receipt of this letter. Your response should describe the specific actions you are undertaking to bring your firm into compliance with the Act and to prevent future violations of law. If you cannot complete all corrections before you respond, you should state the reason for the delay and the time necessary to complete the corrections. If you have already not done so, please include copies of any documentation demonstrating that you have corrected any of the violations listed above. Please direct your reply to Kirk D. Sooter, Compliance Officer, U.S. Food and Drug Administration, 10 Waterview Boulevard, Third Floor, Parsippany, New Jersey 07054. If you have any questions concerning any issue in this letter, please contact Mr. Sooter at (973) 526-6008.

Sincerely yours,

A handwritten signature in cursive script that reads "Douglas I. Ellsworth".

Douglas I. Ellsworth
District Director