



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Mid-Atlantic Region

D1216 B

Telephone (201) 331-2906

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

February 24, 1997

WARNING LETTER

RELEASE

REVIEWED BY

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2/25/97

Robert Vukovich, Ph. D.
President/Chief Executive Officer
Roberts Pharmaceutical Corporation
4 Industrial Way West
Eatontown, New Jersey 07724

Dear Dr. Vukovich:

File No: 97-NWJ-20

This is regarding an inspection of your facility located at 4 Industrial Way West, Eatontown, New Jersey between the dates of October 28 and November 18, 1996. During the inspection our investigators documented serious deviations from the Current Good Manufacturing Practice Regulations (Title 21, Code of Federal Regulations, Parts 210 & 211) in that the controls used for the manufacture, processing, packing or holding of various drug products do not conform to or are not administered in conformity with current good manufacturing.

These deviations were noted on the FDA-483 presented to Drew Karlan, Vice President, Worldwide Regulatory Affairs at the close of the inspection on November 18, 1996. These CGMP deficiencies cause your drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act as follows:

1. Your firm extended the expiration dating period assigned to Topicycline for Topical Solution, (Topicycline), lots 111282 and 61133, from 24 months to 48 months, without a written stability testing program and without appropriate stability data. Both lots were marketed with a 48 month expiration dating period although your firm lacked stability data that demonstrates that Topicycline will continue to meet all of its specifications through a 48 month period. The following was noted:

a. An adequate number of batches were not tested to support expiration dates. Stability testing was conducted by your firm on only two lots of Topicycline, (CN 500243 and CN 500245), to justify a 48 month expiration dating period.

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b. Neither of the two stability lots used to justify the extension of the expiration dating period from 24 months to 48 months, (lots CN 500243 and CN 500245), were tested through a 48 month period.

For lot CN 500243, stability testing was conducted through approximately 46 months only. In your firm's 1994 annual report to FDA, the 5/94 test date and eight week reconstituted sample test date of 7/94, are represented as testing conducted at 48 months and 50 months. However, on 5/94 and 7/94, only 44 and 46 months elapsed since the initial test date, 9/90.

For lot CN 500245, stability testing was conducted through approximately 40 months. In the 1994 annual report, the 5/94 test date and eight week constituted sample test date of 7/94, were represented as testing conducted at 45 and 47 months. However, on 5/94 and 7/94, only 38 and 40 months elapsed since the initial test date, 3/91.

The time-zero starting point of the stability study should be based on the date that samples of the drug product, in its marketed package, are placed under stability study conditions. It is not appropriate to base the start of the stability study on the date of manufacture, which presumably is the starting date for the initial compounding of the batches, and which does not represent the stability of the finished drug product in its marketed package.

c. For stability lot CN 500243, the stability sample tested at 26 months was out-of-specification for Sodium Bisulfite content. Your firm neglected to conduct an investigation to determine the probable causes of the failure to meet specifications.

d. For lot CN 500245, the stability sample tested at the 14 month test interval was out-of-specification for Sodium Bisulfite content. Samples tested at the 24 and 26 month test intervals were out-of-specification for 4-ETC/TC ratio. Your firm neglected to perform any investigation to determine the probable causes of these failures.

Additionally, out-of-specification results for 4-ETC/TC ratio at the 24 month test interval were averaged with passing results derived from testing a second sample. In the 1994 annual report submitted to FDA, your firm reported the passing average value

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only, without any mention of the initial failures. As mentioned above, no investigation was conducted to determine the probably causes of failure.

In the 1994 annual report, your firm commented that for lot CN 500245, the out-of-specification value for 4-ETC/TC ratio at 26 months does not represent a trend of instability, since this is in conformity with the typical behavior of a drug once the expiration date is reached. However, your firm subsequently extended the expiration dating period for Topicycline from 24 months to 48 months without determining the probable causes of failure.

e. Topicycline lot 61133, marketed with an extended expiration date of 2/97, failed to meet stability specifications through out expiry. Out of specification results were obtained on eight week reconstituted samples for Sodium Bisulfite and Tetracycline HCl in 1/95 and for Sodium Bisulfite in 10/96. No action was taken regarding the marketed product.

Please be advised that an official drug (i.e., a drug purported to be or represented as a drug the name of which is recognized in a official compendium) is adulterated within the meaning of Section 501 (b) of the Food, Drug, and Cosmetic Act if it fails to conform to compendial standards of quality, strength, or purity, unless the product label clearly states how it differs from the standard.

2. Your firm has not designated a quality control unit to be responsible for approving or rejecting drug products manufactured, processed, packed or held under contract by another company. The following was noted:

a. There were no written procedures defining the authority, responsibilities, and procedures applicable to a quality control unit. Marketed drug product matters were handled by one group while other quality control unit functions, such as approving changes in manufacturing procedures, were handled by other personnel. There were no written procedures defining how these quality functions should be handled.

b. Your firm has no system for evaluating the quality of drug products manufactured by contract manufacturers. The release and rejection of product lots is determined by the contract

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manufacturer. There is no system for assuring that contract manufacturers and testing laboratories operate in compliance with current good manufacturing practices.

c. Production records are not routinely reviewed to assure no errors have occurred or, if errors have occurred, that they have been fully investigated.

We suggest that you evaluate the number of personnel assigned to quality functions to assure your firm maintains an adequate number of qualified personnel to manage the required functions of a quality control unit.

3. Your firm lacks a training program to assure employees are trained in and remain familiar with the requirements of current good manufacturing practices as they relate to each employee's functions.

4. The Standard Operating Procedure for Customer Complaints (SOP NO. [REDACTED] Rev. 3/9/95) does not require review by the quality control unit or contain provisions for review to determine whether the complaint represents a serious and unexpected adverse drug experience. The form designated in the SOP for documenting the receipt of complaints was not always completed. The current system does not provide for tracking of the complaints to assure documentation and follow-up of each complaint within an appropriate time frame. There are no procedures established to assure responsible individuals, if not personally involved or immediately aware, are notified in writing of any investigations conducted.

5. The syringe supplier for Supprelin Injection was changed due to a product complaint. There was no documentation indicating qualification of the new supplier or assurance that the problem had been corrected by this change.

The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure adherence with each requirement of the Good Manufacturing Practice Regulations. Federal agencies are advised of the issuance of all warning letters about drugs so that they may take this information into account when considering the award of contracts. Additionally, pending Antibiotic Form 6, NDA, ANDA or export approval requests may not be approved until the above violations are corrected.

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You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Possible actions include seizure and/or injunction.

Please notify this office in writing within 15 working days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to prevent the recurrence of similar violations. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time needed to complete the corrections.

Your response dated February 13, 1997 has been received and is currently under review. Please submit any additional comments to: Food and Drug Administration, 10 Waterview Blvd., 3rd Floor, Parsippany, New Jersey 07054, Attention: Diane Edson, Compliance Officer.

Sincerely,


STEVEN MASIELLO
Acting District Director
New Jersey District

CERTIFIED MAIL -
RETURN RECEIPT REQUESTED

DCE:np