



DEPARTMENT OF HEALTH & HUMAN SERVICES

M3257M

New York District

Food & Drug Administration
850 Third Avenue
Brooklyn, NY 11232

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mary B. Harmon
Chairman of the Board and Senior Officer
Thames Pharmacal Co., Inc.
2100 Fifth Avenue
Ronkonkoma, NY 11779

December 17, 1999

Ref: NYK-2000-12

Dear Ms. Harmon:

During an inspection of your drug manufacturing facility located in Ronkonkoma, New York conducted September 9 through October 14, 1999, our investigators documented deviations from the Current Good Manufacturing Practice for Finished Pharmaceuticals Regulations (Title 21, Code of Federal Regulations, Parts 210 and 211). These deviations cause your drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act). The deviations include, but are not limited to, the following:

1. Failure to thoroughly investigate any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications and to make a written record of the investigation including conclusions and follow-up as required by 21 CFR 211.192. For example, there were no documented investigations of the failures of hydrocortisone 1% and acetic acid 2% otic solution, USP (lot nos. K493 and K535) to meet assay specifications at 18 and 24 months stability testing and the failures of acetic acid glacial 2% otic solution, USP (lot nos. J466, H187, and K572) to meet assay specifications at 18 and/or 24 months stability testing. Further, there was no documented investigation of the failure of hydrocortisone cream 1%, USP equipment cleaning validation swab samples to meet microbial test specifications.
2. Failure to maintain complete records of all stability testing performed in accordance with 21 CFR 211.166 as required by 21 CFR 211.194(e). For example, there was no assay data recorded in the analyst's notebook for the 24 months stability testing performed for hydrocortisone 1% and acetic acid 2% otic solution, USP (lot nos. K493 and K535).
3. Failure to submit ANDA field alert reports to the FDA district office as required by 21 CFR 314.98. For example, no field alerts were submitted for the failures of hydrocortisone 1% and acetic acid 2% otic solution, USP (lot nos. K493 and K535) to meet specifications at 18 months stability testing and the failures of acetic acid glacial 2%

otic solution, USP (lot nos. J466, H187, and K572) to meet specifications at 18 and/or 24 months stability testing.

4. Failure to use the results of stability testing to determine appropriate storage conditions and expiration dates as required by 21 CFR 211.166(a). For example, the expiration date for hydrocortisone 1% and acetic acid 2% otic solution, USP was extended from 18 to 24 months despite the failure of two of three batches (lot nos. K493 and K535) to meet assay specifications at 18 months stability testing.
5. Failure to establish and follow adequate laboratory control mechanisms as required by 21 CFR 211.160(a). For example, your QC laboratory failed to follow written sampling plans for retesting acetic acid glacial 2% otic solution, USP (lot no. K572) that failed to meet specifications at 18 months stability testing. Further, SOPs for testing and standardizing stock standard solutions and commercial volumetric solutions were inadequate to determine their suitability for use after prolonged storage.
6. Failure to calibrate laboratory instruments at suitable intervals in accordance with established written procedures as required by 21 CFR 211.160(b)(4). For example, the Karl Fisher automatic titrator and auxiliary reagent syringe were not periodically calibrated. The calibration procedure for the UV spectrophotometer uses a single wavelength accuracy limit that differs from the instrument manufacturer's written specification.
7. Failure to follow established test methods used for the acceptance of drug components as required by 21 CFR 211.160(b)(1). For example, there was no assurance that specific rotation determinations for bulk hydrocortisone acetate (lot no. R6279) were performed at temperatures specified in the USP monograph.
8. Failure to maintain written records of major equipment cleaning, maintenance, and use as required by 21 CFR 211.82. For example, the logbook for recording routine maintenance and repairs for all manufacturing equipment prior to November 1998 could not be located. Further, the purified water system logbook did not record the dates ion exchange beds were changed between July 1996 and December 1998.
9. Failure to assure that equipment cleaning procedures are adequate to prevent the contamination that would alter the safety, identity, strength, quality, or purity of drug products as required by 21 CFR 211.67. For example, cleaning validation surface sampling procedures did not include detailed instructions as to the size of the area to be swabbed. There were no recovery studies to determine the adequacy of the swab sampling method to recover residues. Further, the SOP for cleaning production tanks and kettles lacked detailed instructions as to when detergent may be necessary and the SOPs for changing UV lights in the purified water system and for sanitizing and storing water transfer hoses were not being followed.

10. Failure to include in the batch production and control records complete information relating to the production and control of each batch as required by 21 CFR 211.188(b). For example, there was no record identifying the specific point-of-use for purified water used in production or for equipment cleaning.
11. Failure to limit access to label storage areas to authorized personnel as required by 21 CFR 211.122(d). For example, during the inspection there was a room used for finished product labeling that was unlocked and there was no sign to indicate limited access.

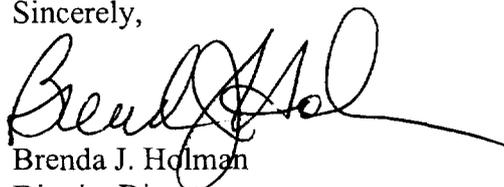
Neither the above identification of CGMP violations nor the inspectional observations (a copy of the Form FDA 483 is enclosed) presented to Mr. Srinivasa Rao, Director, Regulatory Affairs at the conclusion of the inspection is intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence with each requirement of the Act and its implementing regulations. Federal agencies are advised of the issuance of all warning letters about drug products 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.

You should take prompt action to correct these violations. Failure to promptly correct these violations may result in regulatory action without further notice. These actions include, but are not limited to, seizure and injunction.

You should notify this office in writing, within 15 working days after receipt of this letter, of (1) each step that has been or will be taken to completely correct the current violations and to prevent the recurrence of similar violations; (2) the time within which the corrections will be completed; (3) any reason why the corrections have not been completed within the response time; and (4) any documentation necessary to show the corrections have been achieved.

Your reply should be sent to the attention of Bruce A. Goldwitz, Compliance Officer, Food and Drug Administration, 850 Third Avenue, Brooklyn, NY 11232, Tel. (718) 340-7000 ext. 5507.

Sincerely,



Brenda J. Holman
District Director

Enclosure: Form FDA 483 dated October 14, 1999