



DEPARTMENT OF HEALTH & HUMAN SERVICES

T2100M  
New York District

Food & Drug Administration  
850 Third Avenue  
Brooklyn, NY 11232

**WARNING LETTER**

**CERTIFIED MAIL**  
**RETURN RECEIPT REQUESTED**

Robert M. Morrow  
President and CEO  
Thames Pharmacal Co., Inc.  
2100 Fifth Avenue  
Ronkonkoma, NY 11779

October 6, 1998

Ref: NYK-1999-1

Dear Mr. Morrow:

During an inspection of your drug manufacturing facility located in Ronkonkoma, New York conducted on July 22 through September 16, 1998, our investigators documented deviations from Current Good Manufacturing Practice (CGMP) 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 follow written procedures for sampling and testing drug products prior to release for distribution, and to reject those drug products failing to meet established standards and specifications as required by 21 CFR 211.165. For example, fluocinolone acetonide solution (lot #M201) failed initial and repeat assay for strength. The lot was assayed a third time, contrary to the firm's SOP for out of specification results, and subsequently released for distribution based on the third assay. There was no recorded justification for deviating from the established SOP as required by 21 CFR 211.160(a).

2. Failure to establish and follow adequate written procedures for monitoring storage conditions for samples retained for stability testing as required by 21 CFR 211.166(a). For example, out of specification temperature and relative humidity chart recordings were not identified, investigated, and evaluated as to their impact on product stability; incorrect recorder charts were used in the temperature/relative humidity recorder unit for the accelerated studies storage chamber; the alarms on temperature monitors in the ambient temperature stability room were set in the off position; the firm's stability SOPs fail to identify alert and action limits, and remedial actions to be taken when limits are reached; and weekly monitoring of the temperature in the ambient temperature stability room was not performed and documented between February 20 and July 20, 1998.

3. Failure to exercise adequate controls over labeling materials issued for use in drug product packaging and labeling operations as required by 21 CFR 211.125. For example, incorrect labeling materials were issued and later used in the packaging and labeling of batches of tolnaftate cream (lot #s M211 and M255), triamcinolone acetonide cream (lot #M267), and hydrocortisone cream (lot # K500). The failure to carefully examine the labeling materials for identity prior to issuance resulted in labeling mixups and subsequent release and distribution of mislabeled products.

4. Failure to adequately examine packaging and labeling materials for suitability and correctness before packaging and labeling operations as required by 21 CFR 211.130. For example, incorrect labeling materials were accepted and used in the packaging and labeling of batches of tolnaftate cream (lot #s M211 and M255), triamcinolone acetonide cream (lot #M267), and hydrocortisone cream (lot # K500). The failure to carefully examine the labeling materials for suitability and correctness before packaging operations resulted in labeling mixups and subsequent release and distribution of mislabeled products.

5. Failure to routinely calibrate, inspect, or check automatic, mechanical, or electronic equipment used in the manufacture, processing, packing, and holding of drug products according to a written program designed to assure proper performance and to maintain written records of these calibration checks and inspections as required by 21 CFR 211.68(a). For example, bar code readers on various packaging and labeling equipment were not operational during undetermined periods in 1997 and 1998. The inoperable bar code readers failed to detect incorrect labeling materials used in the packaging and labeling of batches of tolnaftate cream (lot #s M211 and M255), triamcinolone acetonide cream (lot #M267), and hydrocortisone cream (lot # K500). The failure to detect the incorrect labeling materials resulted in labeling mixups and subsequent release and distribution of mislabeled products. Further, there were no calibration schedules for certain manufacturing equipment, and calibration reports with out of specification results from outside contractors (e.g., QA003 and QA006) were not investigated and evaluated to determine their impact on drug products. The investigators also observed that the QC laboratory's calibration weights were not certified since April of 1995. The laboratory balances are calibrated with a minimum 100 mg. weight when they are routinely used to weigh standards and samples of less than 10 mg.

6. Failure to maintain a written record of each complaint received in a file designated for drug product complaints as required by 21 CFR 211.198. For example, the firm's complaint file and complaint log failed to include complaints of mislabeled product received in 1997 and 1998 that subsequently resulted in drug product recalls. Further, the firm's SOP for handling complaints failed to specify that all complaints should be maintained in a designated file.

7. Failure to evaluate, at least annually, the quality standards for each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures as required by 21 CFR 211.180(e). For example, the investigators' review of 1997 batch records revealed numerous instances of out of specification manufacturing, filling, and

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packaging yields. This data was not evaluated to identify possible common causes and corrective actions.

8. Failure to retest or reexamine drug components after storage for long periods or under conditions that might adversely affect the components as required by 21 CFR 211.87. For example, the investigators observed raw materials in release status that were past their reevaluation dates or bore incorrect reevaluation dates. These included, but are not limited to, albuterol sulfate (RM #R5677), clindamycin phosphate (RM #R5673), nystatin (RM #R5986), and benzoic acid (RM #s R4360 and R4887).

9. Failure to establish, follow, and document adequate laboratory controls for the use of in-house reference standards as required by 21 CFR 211.160(a) and 211.194(c). For example, there was no SOP for the qualification and use of in-house reference standards; the firm's log of reference standards was not current and contained numerous reference standards that were past their expiration date; reference standards were stored contrary to recommended conditions stated on the label; reference standards were not always dried prior to use; the sodium carbonate primary standard was a mixture of two lots from two suppliers, neither of which was certified as a primary standard; and there was no data to support the shelf-life of standard solutions that were stored and used for extended periods of time.

10. Failure to establish, follow, and document adequate laboratory controls for the calibration of instruments as required by 21 CFR 211.160(b)(4). For example, there were no SOPs for the calibration and/or operation of liquid chromatographs, gas chromatographs, and the infrared spectrophotometer; the SOP for the calibration of the ultraviolet spectrophotometer was not updated for firm's newer ultraviolet spectrophotometer; and there was no SOP for tracking instruments that fail to meet established specifications.

11. Failure of the laboratory records to include complete data derived from all tests as required by 21 CFR 211.194. For example, the reference standard lot number and date of testing were not always recorded in the laboratory notebook; and chromatograms were voided without documenting the reasons for voiding them.

Neither the above identification of CGMP violations nor the inspectional observations (a copy of the Form FDA 483 is enclosed) presented to you 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.

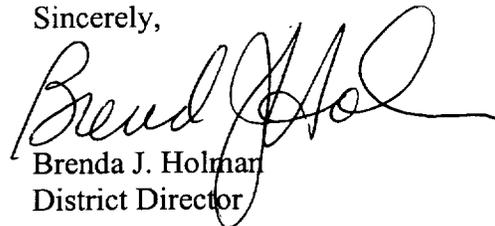
You should take prompt action to correct these violations. Failure to promptly correct these violations may result in regulatory action without further notice. These actions include, but are not limited to, seizure and injunction.

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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 corrective action has 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

Attachment: Form FDA 483 dated September 16, 1998