



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Atlanta District Office

M1993N

301

60 8th Street, N.E.
Atlanta, Georgia 30309

August 7, 1998

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Raymond Holman
President/CEO
Mallinckrodt Inc.
675 McDonnell Boulevard
St. Louis, Missouri 63134

WARNING LETTER

Dear Mr. Holman:

An inspection of your drug manufacturing facility located in Raleigh, North Carolina, was conducted between June 22 and July 2, 1998, by Investigators Kristen D. Evans and Leah M. Andrews. Our inspection revealed several significant deviations from the Current Good Manufacturing Practice Regulations (GMPs) as set forth in Title 21 of the Code of Federal Regulations (21 CFR), Part 211. These deviations cause your parenteral drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (the Act).

You have failed to appropriately respond to out-of-specification (OOS) conditions which could directly impact upon the quality of released product. You have failed to consistently react to, investigate and correct OOS conditions noted during packaging inspection. You could not provide adequate documentation to justify this lack of response to internal reject limits which were exceeded. These limits included those established for particulates, glass particles, and seal defects.

The OOS conditions are not routinely recorded and documented on the Reject Limit Response form as required by Mallinckrodt procedure. Of the approximately thirty lots noted by our investigators to have OOS findings, only twelve such forms were filed. Most of the OOS lots reviewed by the investigators did not have documented investigations or any record of corrective actions taken. Your firm was noted to routinely release the OOS lot without further reprocessing, rework, or an independent verification by quality assurance of the lot. Of the thirty lots reviewed, only two lots included sampling by quality assurance to verify the quality of the lot prior to release.

The written procedure "Listing of Internal Reject Alert Levels and Action Steps if Levels are Exceeded during Packaging" provided conflicting instructions as to the actions required when "other" defects were encountered. The procedure was not clear as to when managers should be notified of "other" defects and what constituted a significant quantity of such defects. Lot X044A was noted to have twenty two rejected vials due to "other " defects. The production records include no indication of the nature of the defects and lack documentation that any managers were notified of the defects.

This failure to document that appropriate corrective actions had been implemented and completed was noted in several significant areas and departments at your firm. This failure was noted after investigations undertaken in response to problems or failures noted in sterility testing, chemistry testing, microbiological testing of pre-autoclaved product, complaint follow-up, and water testing. There was no system in place to assure that corrective actions were implemented and communicated to your employees. Although suggested corrective actions were recorded in some instances, no further action was taken. There were no established time frames for the institution of a corrective action.

You have failed to conduct the required evaluation, at least annually, of the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures. Annual product reviews have not been conducted for all products since 1990, with the exception of a review for Optiray in 1994 and Hexabrix in 1997. The decision to ignore this requirement was a deliberate one reportedly made on the basis of limited resources. You have also failed to visually examine a representative number of reserve samples at least annually as required. No examination of reserve samples is currently performed unless the lot is associated with a complaint.

You have failed to implement appropriate controls to ensure that all drug components and closures have the appropriate quality and purity when introduced into production. You have failed to validate the washing process used for rubber closure components (stoppers, pistons, and caps). The sequence of processing steps to include [REDACTED] has never been validated by your firm to be effective in reducing endotoxin levels of these components. Problems were also noted with the 1998 requalification of [REDACTED] utilized for 50 ml. syringes. The validation cycle used exceeded the minimum cycle specification by 40%. The report for this study did not include all acceptance criteria listed in the procedure.

You have failed to properly maintain production and process control procedures to assure that they remain updated and applicable to current operations. The procedure for the operation of the [REDACTED] washer on line four is not an accurate reflection of existing operations. The procedure refers to valves which no longer exist (including a valve that was removed in 1992), does not include all of the operations expected of the operator, and does not incorporate the operation of a recently installed chart recorder. An unapproved, uncontrolled procedure for the recorder was noted to be posted on the equipment. This was the only equipment operation procedure which was reviewed in depth during the current inspection.

Serious deficiencies were also noted pertaining to the operation and maintenance of the above washer used for the cleaning and depyrogenation of plastic syringes. The current Piping and Instrumentation Diagram for the equipment could never be located during the inspection. The piping configuration for the rinse Water for Injection (WFI) included a large dead leg due to the presence of an inverted filter housing which is not drained after use. Several valves and the sampling port were not physically labeled. In addition, several leaking valves and fittings were noted on the WFI piping. These valves were not part of the preventative maintenance program at the firm.

You have failed to establish written maintenance and calibration programs for all laboratory equipment. Equipment which is maintained and calibrated by outside vendors, such as HPLCs, are not included in the existing programs. There is no system in place to assure that appropriate calibration and maintenance operations are performed. Deficiencies were also noted in the installation qualification (IQ) and operation qualification (OQ) of two recently installed laboratory instruments. There was no procedure requiring IQ/OQ for laboratory equipment.

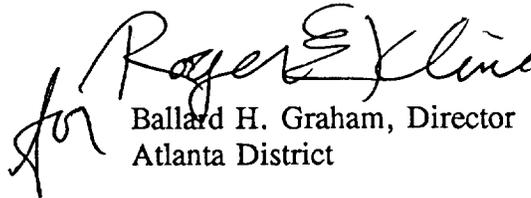
You have failed to assure that laboratory records include complete data derived from all tests necessary to assure compliance with established specifications. The worksheets used for endotoxin testing do not document that the test specification for incubation has been met. This information is recorded on a scrap piece of paper which is routinely discarded. There is also no system established for maintaining the accountability of laboratory worksheets. These worksheets are issued as photocopies of the master worksheet. There is no system in place to assure the accountability and integrity of this laboratory raw data.

Many of the above deviations were included on the FDA 483 (Inspectional Observations) which was issued to and discussed with Christopher L. Guerdan, Director of Site Operations, at the conclusion of the inspection. A copy of the FDA 483 is enclosed for your review. The violations noted in this letter and in the FDA 483 could be symptomatic of serious underlying problems in your firm's manufacturing and quality assurance systems. The deviations discussed above and included on the FDA 483 should not be construed as an all inclusive list of violations which may be in existence at your firm. It is your responsibility to ensure adherence to each requirement of the Act.

You are responsible for investigating and determining the causes of the violations identified by FDA. You should take immediate actions to correct these violations. We acknowledge receipt of an initial limited response to the FDA 483 from Mr. Guerdan dated July 14, 1998. We also have received a more detailed response to the FDA 483 from William Holden, Site Quality Manager, dated July 23. The most recent response is currently under review. These responses will be addressed in future correspondence from FDA. Failure to promptly correct these deviations may result in legal sanctions provided by the law such as product seizure and/or injunction, without further notice to you. Federal agencies are advised of the issuance of all warning letters involving drugs so that they may take this information into account when considering the award of contracts.

You should notify this office in writing, within fifteen (15) working days of receipt of this letter, of any additional steps you have taken to correct the noted violations, including an explanation of each step being taken to prevent the recurrence of similar violations. You may refer to either of the above responses if you feel they adequately address the deviation. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which corrections will be completed. Your response should be addressed to Philip S. Campbell, Compliance Officer, at the address noted in the letterhead.

Sincerely,

for Roger E. Kline
Ballard H. Graham, Director
Atlanta District

Enclosure

cc: Christopher Guerden
Director of Site Operations
Mallinckrodt Inc.
8800 Durant Road
Raleigh, NC 27661