DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Central Region m 3450n

Food and Drug Administration
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Telephone (973) 526-6005

March 2, 2000

WARNING LETTER

Mr. Martin Sperber
Chairman and Chief Executive Officer
Schein Pharmaceutical, Inc.
100 Campus Drive
Florham Park, New Jersey 07932

FILE NO: **00-NWJ-22**

Dear Mr. Sperber:

An inspection of your sterile drug manufacturing facility, Marsam Pharmaceuticals, Inc. (Marsam) located on Olney Avenue in Cherry Hill, New Jersey, and conducted by Food and Drug Administration investigators between March 25 and July 29, 1999, found significant deviations from current Good Manufacturing Practice (cGMP) regulations for Finished Pharmaceuticals (Title 21, Code of Federal Regulations, Part 211). Such deviations cause finished pharmaceuticals to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act.

The following summarizes the most egregious cGMP violations observed at Marsam:

1. The firm ignored initial out-of-specification results, performed retesting, and released product for distribution without conducting adequate laboratory investigations. In one instance, the Director of Quality Control crossed out the analyst's statement of true results and determined the low results were due to laboratory error without any evidence or investigation of the results. Specifically, Cefazolin Sodium, USP 10 g/100 ml, lot 9708060 failed an initial assay. A second test on new preparations from the original sample was performed. The preparations consisted of a first and second dilution and a new sample preparation from the original solution. All three preparations failed. The investigation into the failing results could not identify any laboratory errors. The Director of Quality Control crossed out the analyst's statement: "This proves that there was not an analyst error." The Director concluded that the cause of the failing result could not be determined but checked off that a laboratory error was identified. There was no further investigation into this matter. The failing results were rejected and replaced with passing assay values from a new tray. The lot was passed and released.

2. The written stability program is deficient in that the potency determinations for injectible Cefuroxime Sodium and Cefazoline Sodium are done on reconstituted solutions that have been stored at room temperature for at least 24 hours and does not include testing the drug product immediately after reconstitution.

3. Laboratory controls are deficient in that the firm established a written procedure, which allowed for the averaging of out-of-specification and within-specification analytical test data results, as was done with Ampicillin for Injection 10 gram/100ml vial, lot 9710002.

4. The Quality Control Testing Laboratory deviated from approved USP test methodologies for purity and potency by using external heating columns, instead of performing the tests at room temperature as required. The actual temperatures and the use of external heater columns were not documented for at least two lots of Sterile Cefazoline Sodium, U.S.P., and the effects of temperature variations were not studied during validation.

5. The Quality Control Unit failed to:

   a) Evaluate the solubility of the ingredients used such as Etoposide in the sterile liquid injection products; and to investigate the oily black residue found during the cleaning re-validation study for Morphine Sulfate Injection, USP.

   b) Perform cleaning validation studies for Neostigmine Methylsulfate Injection USP, and Heparin Injection USP.

   c) Conduct adequate studies to determine the effectiveness of the cleaning procedures to control microbial contamination of non-sterile products, and to conduct adequate studies to determine the effectiveness of the sterilization and depyrogenation procedures on equipment surfaces that contact sterile products.

   d) Conduct adequate studies to determine the effectiveness of sanitizing agents against indigenous (firm's bioflora) and USP indicator organisms, and to set appropriate time limits for the application of the cleaning agents.

6. Failure to maintain the integrity and adequacy of the laboratory's computer systems used by the Quality Control Unit in the analysis and processing of test data. For example:

   a) There was a lack of a secure system to prevent unauthorized entry in restricted data systems. Data edit authorization rights were available to all unauthorized users, not only the system administrator.

   b) The microbiology department's original reports on sterility test failures of Penicillin G Potassium for Injection, lots 9804024 and 9811016 due to environmental mold, which were sent via electronic mail to the Quality Assurance Management, differed significantly from the versions included in the Quality Assurance Management's official reports.

   c) The network [redacted] module design limitations, which can only support up to four chromatographic data

acquisition systems, had up to five chromatographic systems connected. There was no validation showing this configuration to be acceptable.

d) System testing was not conducted to insure that each system as configured could handle high sampling rates. Validation of the systems did not include critical system tests such as volume, stress, performance, boundary, and compatibility.

7. There was a failure to thoroughly investigate and document unexplained discrepancies or batch failures. For example:

a) Management failed to adequately follow-up on failure investigation reports, including sterility failures due to mold and bacteria. Various batches were released upon re-testing, with each of these failures attributed to inadvertent contamination while performing the sterility test, yet, there is little to no data available to support this conclusion. The investigations failed to address the correlation between microorganisms found in the manufacturing environment and those found in units that initially tested positive.

b) In addition, the firm failed to document the location on the drywall from where a sample with mold contamination was taken. The raw data for the microbial testing of the drywall was lost and there was no investigation into whether there was a correlation between the sterility positives and the environmental samples that exceeded limits for mold.

8. Written cleaning procedure SOP XII-016-03, Cleaning and Sanitization of Sterile Filling Areas, calls for the vacuuming and sanitizing of equipment and the mopping of floors. Management failed to assure that this procedure was being followed in that accumulated residues were observed on and under filling equipment in Sterile Filling Room 41.

9. The building used in the manufacture and processing of the sterile drugs was deficient in that:

a) The sterile core in the sterile powder drug products filling areas had epoxy paint peeling off the walls, cracks in the floor, holes in the walls, and rough surfaces on the floors and in the corners of the rooms.

b) In addition, terminal HEPA filters did not sit flush in the supports, masking tape was found on equipment, and stainless steel window framing had separated from the window.

10. Failure to establish and follow adequate written procedures for cleaning and maintenance of equipment. For example:

a) The class 100 area in Filling Room 41 used for the manufacture of sterile drug products was not maintained in a clean and sanitary condition, even after having been cleaned and sanitized five times and after being found acceptable by the Quality Control Unit.

b) In addition, the employees responsible for sanitizing the sterile core failed to follow cleaning procedures due to their fear of electrocution because of exposed wiring under the powder-filling machine.

11. Equipment used in the manufacturing and processing of a sterile drug product was not of appropriate design to facilitate cleaning and maintenance. For example, as a result of the exposed wiring, the class 100 area could not be properly cleaned and sanitized.

The above is not intended to be an all-inclusive list of violations. As a manufacturer of finished pharmaceuticals, you are responsible for assuring that your overall operation and the products you manufacture and distribute are in compliance with the law.

Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these violations and to establish procedures to prevent their recurrence. Failure to promptly correct these violations may result in regulatory action without further notice, such as seizure and/or injunction.

We recognize that Schein Pharmaceutical, Inc. has voluntarily initiated the following actions in response to the inspection:

- Ceased all production at the Marsam facility.
- Committed to resume manufacturing only after all the issues have been addressed to the satisfaction of the agency.
- Evaluated management's responsibility for the problem areas and instituted corrections.
- Voluntarily recalled all products still within expiry.
- Voluntarily destroyed or scheduled for destruction undistributed and returned product.
- Hired an outside consultant to develop a Corrective Action Plan.

We are in receipt of your firm's September 29, 1999 written response to the observations noted on the Inspectional Observations Form FDA-483 and your Corrective Action Plan. We are withholding comment in view of statements made by Mr. Donald A. Britt, Senior Vice President, Quality and Regulatory Compliance, during his visit to this office on January 31, 2000 and in his follow-up letter of February 7, 2000, that the response may be modified. We have also received Dr. William McIntyre's letter of February 17, 2000 requesting a meeting with Agency representatives. That meeting is tentatively scheduled for March 8, 2000 at the New Jersey District Office.

We have been advised of your plan to renovate building 31 during a meeting with Schein representatives held on January 12, 2000 at our North Brunswick Resident Post. We understand that future production in 31 South is uncertain. Mr. Britt mentioned during his visit that the start up process will likely focus on [redacted] In any event, when manufacturing penicillin products you should consider the separation requirements of Title 21 Code of Federal Regulations, Sections 211.42(d), 211.46(d), and 211.176. The adequacy of the separation between penicillin and non-penicillin products should be evaluated. A lack of adequate separation and containment can create a potential for cross contamination of the non-penicillin products within building 31, and other manufacturing sites within the Marsam facility. There should be physical and air handling separation, and containment controls. Containment means no movement of personnel, equipment, and materials between the North and South parts of the building, and other manufacturing buildings.

We are concerned about the final disposition of the Penicillin G (Potassium and Sodium) injectible products as well as the injectible Cefuroxime Sodium and Cefazoline Sodium products.

Marsam Pharmaceuticals, Inc.
Cherry Hill, New Jersey 08034

We have noted from the various documents we have received from Dr. Thomas Culkin, Director, Regulatory and Professional Affairs, that the bulk of these products have not been scheduled for destruction. These products were manufactured in building 31 under the cGMP deficiencies cited above. We see no difference in regulatory status between these products and those that have been voluntarily destroyed.

Until the District has determined that your firm is in compliance, the District will not recommend approval of any applications listing your facility as a manufacturer of sterile and non-sterile pharmaceuticals.

We request that you reply in writing within 15 working days of the steps you are taking to correct the violations, or you may present the corrective measures during the March 8, 2000 meeting.

Correspondence concerning this matter should be directed to the Food and Drug Administration, Attention Richard T. Trainor, Compliance Officer.

Sincerely yours,

Douglas I. Ellsworth

DOUGLAS I. ELLSWORTH
District Director
New Jersey District

CERTIFIED MAIL
RETURN RECEIPT REQUESTED