HFD-322 Warning Ltr Book

DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

MAR 25 1998

Pharmacia & Upjohn N.V./S.A.
Rijksweg 12
B-2870 Puurs
Belgium

Dear Mr.

We have completed our review of the inspection of your pharmaceutical manufacturing site at Puurs, Belgium on October 6 - 10, 1997, performed by FDA Investigator Richard L. Friedman. This inspection revealed significant deviations from Current Good Manufacturing Practices (CGMPs) in the manufacture of sterile pharmaceutical products. These CGMP deviations cause your pharmaceutical products to be adulterated within the meaning of Section 501 (a)(2)(B) of the Federal Food, Drug and Cosmetic Act.

Our review also included your company's response letters dated October 20, November 5, and December 29, 1997, and January 16, February 23 and February 27, 1998. These responses were also discussed during the meeting with representatives from your firm on March 13, 1998. We note that many corrections have been, or will soon be implemented. Specific areas of concern include, but are not limited to:

1. Procedures were not appropriate for the control of microbiological contamination.

a. Critical contact surfaces in aseptic filling areas were not sterilized prior to each use.

b. Cleaning and sanitizing frequency of non-contact surfaces was not qualified and was not always documented.

c. Design of the aseptic area permitted excessive traffic through filling rooms.

d. Differential pressure between controlled areas was insufficient.

e. Personnel were observed practicing inadequate aseptic procedures.

The corrections described in your responses, if implemented, appear satisfactory to correct these deficiencies, except that the walls in the aseptic filling area should be cleaned and sanitized more frequently The monitoring described in the responses is insufficient to justify this frequency. The responses regarding personnel practices observed during the inspection indicate this deficiency has been corrected by retraining and improving equipment and techniques, and will be evaluated on an annual basis. During the meeting on March 13, 1998, your representatives also stated that employee aseptic practices are observed by supervisory personal and monitored by the Quality Control Unit on a regular basis. Please provide a copy of the SOP which describes QC responsibilities and procedures for monitoring employee practices in the aseptic filling area.

2. Sterility test method validation was incomplete in that the validation study found apparent inhibition of growth in bacteriostasis and fungistasis testing.

Your responses indicate that the appropriate SOPs have been revised to correct this deficiency, but does not address the apparent growth inhibition or confirm that the validation has been repeated for each test method. During the March 13, 1998, meeting, your representatives stated that additional validation studies have been completed. Please submit the results of those studies to our office for review.

3. The system used to produce water used for final rinsing of container-closures and equipment was not designed to, and had not been adequately demonstrated to produce water meeting appropriate microbiological and endotoxin requirements.

Your responses indicate these deficiencies have been corrected by an initial daily monitoring program, which will be followed by a weekly sampling program, and that a new WFI system will be installed and qualified by
During the March 13, 1998 meeting your representatives clarified that the system is designed to prevent adding contamination, and that monitoring will include each point of use on a weekly basis. Please submit a detailed plan which describes all sampling points, sampling frequencies, including special circumstances such as seasonal changes, action limits, and a description of the action to be taken. Also submit the results of the samples taken as of the present time.

4. Monitoring of aseptic personnel was inadequate in that sampling was only performed weekly, action limits were high, and organisms were only identified when results exceed the action limit.

   Your responses indicate you have improved sampling frequencies, lowered action limits, and will identify organisms found in order to correct the listed deficiencies. We remain concerned about the revised action limits for one time and consecutive positives, and when and what type action is triggered. Trends and multiple incidents of contamination, whether they are consecutive or not, should trigger some action. During the March 13, 1998 meeting, your representatives stated that such trending is being performed. Please submit a copy of the SOP which describes these action limits and the actions to be taken.

5. Media fill procedures were inadequate in that they did not include all employees or worst case conditions, or require adequate investigation and corrective action when contamination was detected.

   Your response appears adequate except that it indicates corrective action has been implemented for the investigation of future media fill failures, but does not address any action regarding batches produced between the previous successful media fill and the failed media fill. The response also provides a revised media fill program, but the inspection indicated that the previous program (SOP) was not followed. During the March 13, 1998 meeting, your representatives stated that the new written procedure includes details which will prevent recurrence of this deficiency. Please submit a copy of this SOP to this office for review. Adherence to these written procedures will be evaluated during the next inspection.

6. Endotoxin/bioburden had not been evaluated for some components used in sterile products.

The responses regarding these observations are insufficient in that they describe your program to select raw materials for endotoxin testing based on several factors including vendor certifications and historical test data. It did not indicate how vendor certificates will be verified or indicate what historic data will be used in making this decision. For those components which will not be tested, please indicate the reason that no testing is warranted and the documentation used to reach this conclusion.

7. Sterile filtration validation has not been completed for one product.

   The written responses and discussions regarding this deficiency indicates your firm is in the process of taking satisfactory corrective action. Please submit a copy of the final report when the study is completed.

The CGMP deviations identified above or on the FD-483 issued to your firm are not to be considered an all-inclusive list of the deficiencies at your facility. FDA inspections are audits which are not intended to determine all deviations from CGMPs that exist at a firm. If you wish to continue to ship your products to the United States, it is the responsibility of your firm to assure compliance with all U.S. standards for Current Good Manufacturing Practices.

Please respond to this letter within 30 days of receipt. Your response should include copies of SOPs generated as well as data collected in your correction to the deficiencies cited. Please identify your response with Until FDA can confirm compliance with CGMP's and correction to the most recent inspection deficiencies, this office will recommend disapproval of any new applications listing your firm as the manufacturer of sterile drug products. Your firm is considered acceptable as a source of non-sterile pharmaceuticals.

Please contact John M Dietrick, Consumer Safety Officer, at the address and telephone numbers shown above, if you have any questions, written response or concerns regarding these decisions.

Sincerely,

Joseph C. Famulare

Joseph C. Famulare, Director
Division of Manufacturing and Product
Quality, HFD-320