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HFD-322 WL 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

Ferring AB
Soldattorpsvagen 5
S-200 61 Malmo, Sweden

Dear Mr.

This is regarding an inspection of your sterile pharmaceutical finished dosage form manufacturing facility in Malmo, Sweden, by Investigator David C. Pulham, Ph.D., Microbiologist Kevin Kallander, and Chemist Azza Talaat of the United States Food and Drug Administration, during the period of October 16 - 24, 1997. The inspection revealed significant deviations from U.S. current good manufacturing practice (CGMP) regulations in the aseptic manufacture of sterile pharmaceutical finished products. The deviations were presented to on an Inspectional Observations form *FDA-483 at the close of the inspection. These CGMP* deviations cause your sterile pharmaceutical products to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act.

We have reviewed your November 13, 1997 response to the FDA-483 observations and the December 19, 1997 Status Report. We note that many corrections were implemented or will soon be implemented. We met with you and representatives of your firm on February 11, 1998, to clarify some of the written responses and your action plan and commitments. The commitments made during this meeting appear adequate, if satisfactorily completed, to bring the facility into compliance with CGMP; however, we believe it is important to restate our position regarding the most significant observations:

1.

The is not sterilized between uses or between products, it is only sanitized. The personnel and manipulative activities of chamber loading, and cleaning followed by sanitization and rinsing can increase bioburden levels.

As discussed during the meeting, this cannot be sterilized and should not be used for aseptic processing. Your firm has discontinued using it for all U.S. production until various alterations are completed and it has been re-qualified. You have stated that this will be phased out completely by We recognize the importance of maintaining adequate supplies of this drug product, but request that you submit the qualification data to this office, prior to resuming temporary use of the for U.S. production as scheduled. Documentation should include a diagram of the and test data which demonstrates that the chemical treatment is sufficient to minimize any possibility of microbiological contamination of the product. Your data should include hard to reach areas that are often inaccessible to surface chemical sanitization treatments. In addition to the chamber, some of these areas include the condenser, the piping for the administration of gases for backfill or vacuum breaks, and shelf support rods.

2. Aseptic Facility Design

The aseptic processing areas were not adequately designed and operated to prevent contamination of sterile components and surfaces. For example:

a. Aseptically filled vials held in the area and also in areas lacking unidirectional air flow.

b. Sterile trays and frames are held in a area throughout the filling process, then brought inside the area to be used. Likewise, each bag of sterile stoppers is opened in the area before being loaded into within the area.

c. Filling room operators were observed contacting the wall with their gowns, and interrupting unidirectional air flow with their bodies.

d. The door extended into the area each time it is opened.

e. All personnel passed through one aseptic filling room when entering and exiting other rooms inside the aseptic area.

Your written response describes a three-phase redesign of the aseptic processing areas, with the first phase completed by However, you have not yet provided a completed validation study demonstrating that the corrective actions are adequate for an aseptic processing operation. Your validation study of current and future operations should include air flow (smoke) and product simulation (media fill) studies, and environmental monitoring under dynamic conditions.

3. Gowning Procedures

   Inadequate gowning techniques and inadequate face cover were observed. For example:

   a. The eyes, forehead and cheeks are exposed throughout aseptic filling.

   b. Gowning is done with ungloved hands and the mask, placed over the hood, is not secured.

Your response indicated retraining of personnel, the change of gowning procedures and the purchase of goggles. However, your written response failed to provide a gowning qualification program which demonstrated the ability of the clean room operators to maintain the sterile quality of the gown when performing gowning procedures. The gowning procedures should also include a scheduled periodic requalification to ensure continued acceptability of aseptic gowning techniques. As discussed during the meeting on February 11, 1998, please provide this office with a copy of your revised gowning procedures and a report to demonstrate that the procedure has been fully qualified.

4. Quality Control Unit

   Lack of oversight by the Quality Control (QC) Unit to ensure that controls which assure product quality are implemented during the manufacturing operations. For example:

   a. QC does not release the aseptic filling line prior to each filling operation.

   b. Personnel monitoring is not done by QC, but by production aseptic filling operators themselves.

   c. Out-of-specification in-process fill volume weights were observed selectively being recorded by production personnel causing records to lack fill weight deviations obtained during vial manufacturing.

Your written responses to these observations were inadequate as discussed during the February meeting. As discussed, FDA expects QC to be responsible for personnel monitoring and that all fill volume weights for are recorded without operator intervention or data selection, for review by QC. You stated that these deficiencies have now been corrected and that documentation of the corrections will be submitted. Please submit copies (English translation) of the SOPs or other documents which demonstrate correction of these deficiencies.

5. Filters

The filter integrity and face velocity test results provided in your written response due to the unavailability of these documents when requested during the FDA 10/97 inspection were reviewed and we have the following concerns:

a. The integrity test data for the ceiling filters, and the requirements and each filter's reference location could not be evaluated.

b. The information submitted for the filters in the clean room failed to provide your established air velocity control parameters in order for us to determine whether they were within established velocity limits. There were approximately filter reports reviewed that showed levels much lower than m/s at the filter face, indicating possible lower unacceptable values at the work level. Validation of aseptic processes usually include establishing appropriate air velocity parameters over the critical working level.

As agreed to during the meeting of February 11, 1998, please provide this office with the location and specifications for these filters, and data which demonstrate that the filters meet established specifications.

As discussed during the meeting on February 11, 1998, production of products has been discontinued until the first phase corrections are completed and the facility is qualified. We are also concerned about the production of other aseptically filled, products in this facility before the first phase corrections are completed and the redesign qualification is completed.

The CGMP deviations identified above 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. We recommend that you evaluate your facility on an overall basis for CGMP compliance. It is the responsibility of your firm to assure compliance with U.S. standards for current good manufacturing practices for pharmaceutical manufacturers.

As discussed during the February 11, 1998 meeting, please submit the requested information regarding the outstanding issues discussed above, and continue to notify this office as the specific steps discussed during the meeting are completed. Until FDA has confirmed that these deficiencies have been corrected and your firm is in CGMP compliance, we will not recommend approval of any new applications listing your firm as a supplier of sterile drug products. Failure to complete the corrections discussed may result in further regulatory action.

Please contact Edwin Melendez, Compliance Officer, at the address and telephone numbers shown above if you have any questions. All information requested in this letter and discussed during the February 11, 1998 meeting should be submitted for his review before production resumes as you committed. Also, please reference within your written response.

Sincerely,

Joseph C. Famulare
Director
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CC:

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