



Division of Manufacturing and Product Quality
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JUN 19 1998

Warning Letter

Nycomed-Amersham plc
Amersham Place, Little Chalfont
Bucks HP7 9NA, England

Dear Mr.

This is regarding an inspection of your sterile pharmaceutical manufacturing facility in Gloucester, England, by Investigator Richard Friedman, of the United States Food and Drug Administration, during the period of October 13-17, 1997. The inspection revealed significant deviations from U.S. current good manufacturing practice (CGMP) regulations in the manufacture of sterile pharmaceutical finished products. The deviations were presented to Mr. 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 completed our review of your company's response letters to the FDA-483 observations dated November 10, 1997 and February 11, 1998. We note that many corrections were implemented or will soon be implemented. However, we still have the following concerns regarding the most significant observations:

1. The is every rather than between each use or between products. It is only sanitized between each use.

should be sterilized after each cycle because of the personnel and manipulative activities of loading and cleaning, followed by sanitation and rinsing which can increase bioburden and particulate levels. Your response proposes to increase the interval of the chamber to months. This interval is unacceptable.

Further, your response was insufficient in providing information that the sanitization of the would maintain the sterile condition of the Documentation should include a diagram of the and sampling location should

include hard to reach areas that are often inaccessible to surface chemical sanitizing treatment. In addition to the some of these areas include the and the

You should establish the effectiveness of your sterile sanitizing solution. Please provide evidence showing your sanitizing solution's effectiveness against your normal microbial flora and spore forming microorganisms. Studies have shown that certain organisms develop microbiological resistance to sanitizing agents after prolonged use, therefore disinfecting solutions should be rotated. This is important to assure that disinfectants retain their efficacy against normal microbial flora.

Please provide your sanitizing (disinfecting) procedure and data on the non-viable particulate load within the when manually sanitizing with We are concerned that this practice will leave unacceptable amounts of non-viable particulates in the during the cycles which could migrate into the product in the event of mechanical failures. Also, please indicate whether the procedure provides controls for the number of batches, types of products and interventions required throughout the intervals between the sterilization. If so please provide the data.

2. Equipment surfaces which contact sterile product container-closures are not sterilized prior to each use. The procedures failed to require sterilization of in which sterile stoppers are placed. The are sanitized only with and is only done

Equipment surfaces which contact sterilized drug product or sterilized container/closure surfaces should be sterile. In processing, it is important to validate both the sterilization process for equipment surfaces as well as the sterilization processes for the drug product and the container/closure.

Your response mentions that all equipment surfaces which are considered critical surfaces are routinely monitored for the presence of microbiological contamination prior to use. This is a less than desirable practice which may contaminate product needlessly. You indicate that you include the use of this equipment in however, there are no substitutions for a validated sterilization procedure. Your response indicated that your company was assessing the ability to sterilize equipment which contacts sterile product container/closures in order to determine the most appropriate method of sterilization. You mention for example, the use of or examination of other chemical sterilants. However, no report was provided. Please provide this report, data to support the selection of your disinfecting agent, and a description of the controls used to assure the disinfecting/fumigating agents do not leave residues which could adversely affect the product. The selection of a disinfecting agent should be validated in relation to microbial flora in your area

The USP includes preacceptance testing against indicator organisms prior to introduction of a disinfecting agent into an area. Also, improperly prepared or handled disinfecting agents can themselves lead to contamination.

3. procedures were inadequate in that they did not include the following:
- a. The origin of contaminants that are isolated.
 - b. batch records lacked assignments.
 - c.
 - d. Atypical interventions have only been simulated in a on one occasion. Also the number and type of normal interventions are not routinely simulated.

The corrections described in your response, if implemented, appear adequate to correct these deficiencies, except that the should not be done

It is possible that would be compromised in the process simulation, which is conducted to determine whether personnel or the operation are introducing contamination into the product. The should be qualified separately. Please indicate whether this practice will continue. Further, the response mentioned monitoring of the interventions for and updating procedure to include atypical intervention by April 1998. Please provide a copy of this procedure with your response and indicate whether this practice will continue.

4. had not been evaluated for some components such as actives and excipients used in processed products.

Each lot of a component that is liable to microbiological contamination that is objectionable in view of its intended use shall be subjected to microbiological testing, and for injectables, testing before use.

In your response regarding you describe testing and initiating investigations where values of are found in the finished dosage form. Controls to prevent contamination, particularly for sterile products, should be in place starting with raw materials through finished product. From a CGMP standpoint, it is not appropriate to simply rely upon final product testing.

The responses regarding these observations are insufficient in that they describe your program to select raw materials for testing based on several factors including vendor certifications and historical test data. It did not indicate how

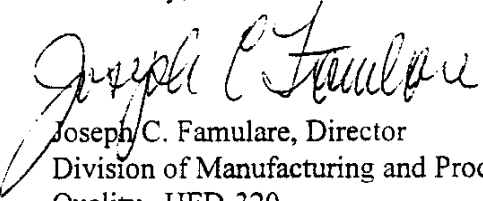
vendor certificates will be verified or indicate what historic data will be used in making this decision. For those components which will not be tested, please indicate the reasons that no testing is warranted and the documentation used to reach this conclusion.

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. We recommend that you evaluate your facility on an overall basis for CGMP compliance.

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 procedures generated as well as data collected in your correction to the deficiencies cited. Please identify your response with CFN 9611191. Until FDA can confirm compliance with CGMP's and correction to the inspection deficiencies, this office will recommend disapproval of any new applications listing your firm as the manufacturer of sterile drug products.

Please contact Edwin Melendez, Compliance 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, Director
Division of Manufacturing and Product
Quality, HFD-320

CC: