HFC-133
Associate Director

DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION CENTER FOR DRUG EVALUATION AND RESEARCH

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FEB 18 1997

WARNING LETTER

Dr. Thomas M. Riedhammer,
President
Dr. Mann Pharma
Brunsbuttler Damm 165
D-W-13581 Berlin, Germany

Dear Dr. Riedhammer:

This is regarding an inspection of your sterile pharmaceutical finished dosage form manufacturing facility in Berlin, Germany, by Investigator Joyce E. Bloomfield and Microbiologist Raymond T. Oji during the period of December 9 - 12, 1996. The inspection revealed significant deviations from U.S. current good manufacturing practice (CGMP) regulations in the aseptic manufacture of sterile ophthalmic solution . The deviations were presented to your attention on an Inspectional Observations form FDA-483 at the close of the inspection. These CGMP deviations cause your sterile ophthalmic products to be unacceptable for use in the United States, since under United States law, those CGMP deviations make your products adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act.

We have reviewed your December 20, 1996 response to the FDA-483 observations submitted to the FDA's Division of Emergency and Investigational Operations, formally International Technical Operations Branch, by Dr. Lothar Wawretschek, VP, Product Quality and Dr. Gerhard Bauer, VP, Operations. We have also evaluated the information provided during the meeting with FDA on February 7, 1997. We note that many corrections were implemented at the conclusion of the inspection or will soon be implemented. However, there are some responses that lack sufficient detail, explanations, or documentation to adequately address the deviations noted during the December 1996 inspection. Our comments regarding the most significant observations are shown below:

VALIDATION/QUALIFICATION

1.

2.

Your response indicates that a validation study for the sanitizing process has been performed; 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 agent does not become contaminated. The selection of a disinfecting agent should be validated in relation to microbial flora in your aseptic area (environmental microorganisms). The USP requires preacceptance testing against "indicator organisms" prior to introduction of a disinfecting agent into an aseptic area. Also, disinfecting agents can themselves lead to contamination.

3.

4.

5.

Your response states that you will conduct a comprehensive prospective validation of this process. However, no validation protocol or summary was provided. Furthermore, our review indicates that individual validation deficiencies are often corrected without a more global approach to achieving comprehensive CGMP compliance. Therefore, please provide your validation procedures outlining your firm's overall program for qualification of equipment and systems, and validation of processes. In general, these procedures should establish your standard approach to validation and address the preparation of validation protocols and reports, as well as revalidation and retrospective validation requirements.

PROCESS DEVIATIONS/FAILURES

assessment indicating that changes in sterilization cycle parameters does not affect the product. Please provide this information, as well as your procedures for addressing any unexplained discrepancy or the failure of a batch or its components to meet specifications.

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.

During the meeting with FDA on February 7, 1997, you indicated that you will provide documentation that corrective action for all deficiencies has been either initiated or completed, and would include a time table and written plans for completion of these corrective actions. Until that documentation is received and found to satisfactorily address these deficiencies, this office will not be able to recommend approval of any applications listing your firm as a supplier of sterile finished dosage forms. As discussed during that meeting, we will evaluate this documentation upon receipt.

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 U.S. standards for current good manufacturing practices for pharmaceutical manufacturers.

Please contact Edwin Melendez, Compliance Officer, at the address and telephone numbers shown above if you have any questions. Within your written response to this letter, please detail corrective actions you plan to take or have taken to bring your operations into compliance. Please include a timetable of when each of the corrections will be completed and attach English translations of supporting documents. Please reference CFN # 9611635 within your written response.

To schedule a reinspection of your facility, after corrections have been completed and your firm is in compliance with CGMP requirements, send your request to: Deborah Browning, Consumer Safety Officer, Drug Group, of FDA's Division of Emergency and Investigational Operations (HFD-133), Division of Field Investiations, 5600 Fishers Lane, Rockville, Maryland, 20857. You can also contact the office at (301) 443-1855 or by FAX at (301) 443-6919.

Sincerely,

Douglas I. Ellsworth,
Director
Division of Manufacturing and
Product Quality, HFD-320