DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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WARNING LETTER

WL: 320-00-05

VIA FEDEX

SEP 19 2000

Dr. Paolo Verardi
Quality Director
Glaxo Wellcome, S.p.A.
Via A. Fleming, 2
37135 Verona, Italy

Dear Dr. Verardi:

We have completed our review of the inspection of your sterile pharmaceutical manufacturing facility in Verona, Italy, by Investigator Richard L. Friedman and Microbiologist James A. Jagow during the period of May 22 to 29, 2000. The inspection revealed significant deviations from current good manufacturing practices (CGMP) in the manufacture of sterile pharmaceuticals. The deviations were presented on an Inspectional Observations (FDA-483) form, 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.

Specific areas of concern include, but are not limited to:

1. The aseptic powder fill process simulation (media fills) did not adequately address several critical issues such as the length of the campaign and the length of time critical equipment is used without re-sterilization, some routine lengthy maintenance interventions and multiple aseptic additions, and maintenance personnel who have access to the aseptic area during filling.

2. Qualification of procedures for sanitizing equipment surfaces was not adequate to ensure an aseptic processing environment.

3. Aseptic procedures intended to prevent microbial contamination of drug products purporting to be sterile were deficient, for example:

a. Operators were observed using non-sterile items while performing interventions on or over sterile products or critical surfaces.

b. Personnel monitoring procedures allow individual operators to be monitored as infrequent as once every [ ] months.

c. Atypical interventions were either not documented or inadequately documented, and written procedures failed to define when an intervention must be documented in the batch record or when a deviation report is triggered.

4. Media used in sterility analysis was not adequately tested for its growth promoting quality

We have also completed review of your response letter dated June 22, 2000 to the FDA-483 observations. These responses were discussed during the meeting with representatives from your firm on August 30, 2000. Additional documentation of corrective actions was then submitted on September 11, 2000, following that meeting. We acknowledge that many corrections have been made and/or are in progress. These corrections, when fully implemented, appear to satisfactorily address the deficiencies listed on the FDA-483. We also note that production of aseptically filled products for the U.S. markets has been suspended until these corrections are completed.

The CGMP deviations identified above or on the FDA-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 provide additional documentation of completion of the media fill studies before aseptic production is resumed. This office will recommend withholding approval of any new applications listing your firm as the manufacturer of sterile drug products until it is received. Implementation of the corrective actions will be further evaluated during the next inspection of this facility. Your firm is considered acceptable as the source of non-sterile pharmaceuticals.

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

CC: Ms. Janice Whitaker
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