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

Division of Manufacturing and Product Quality
Foreign Inspection Team, HFD-322
7520 Standish Place
Rockville, Maryland 20855-2737

TELEPHONE: (301) 594-0095
FAX: (301) 594-2202

FEB 3 2000

Warning Letter

WL: 320-00-01

Giovanni Autelli, Plant Manager
Pharmacia & Upjohn, S.p.A.
Viale Pasteur, 10
20014 Nerviano (Milan), Italy

Dear Mr. Autelli:

This is regarding an inspection of your sterile pharmaceutical manufacturing facility in Nerviano, Italy, by Investigator Gwyn G. Dickinson of the Food and Drug Administration, during the period of April 12-20,1999. The inspection revealed significant deviations from U.S. current good manufacturing practice (CGMP) regulations in the aseptic manufacture of sterile finished products. The deviations were presented to you, 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. Section 501(a)(2)(B) of the Act requires that all drugs be manufactured, processed, packed, and held according to current good manufacturing practice (CGMP).

We have completed our review of your May 10, 1999, response to the FDA-483 observations. We note that many of the commitments made in your response appear adequate, if satisfactorily completed, to bring the facility into compliance with CGMP. There are also issues, which we believe need more comprehensive corrections. Since we have not received documentation that the corrections have been satisfactory implemented, we are restating our position regarding the most significant observations:

1. Facility Design Features

   a. The aseptic processing areas were not adequately designed and operated to prevent contamination of sterile components and surfaces. For example:
      1. Carts containing partially stoppered vials of sterile product enter the class 10,000 area as they are loaded into the lyophilizers.
      2. The lyophilizer doors extend into the class 10,000 area when open.
      3. Aseptic connections of hoses/equipment such as filling nozzles and manifold are made in a class 10,000 area and not in class 100 laminar flow areas.
      4. Air flow studies to assess turbulence and laminarity have not been performed with personnel performing aseptic activities.

b. Access to the aseptic processing areas is inadequate in that after exiting the gowning room, filling room operators must walk up stairs to the second level and enter an upper level corridor prior to entering the filling room. The stairs are equipped with a handrail.

Regarding 3.b, your response indicates additional precautions in this area such as resanitizing sterile gloves prior to entering sterile areas, increased environmental monitoring, including surface sampling of the handrails. The different floor level corridor is a poor design, difficult to sanitize, qualify and monitor. It increases the possibility of contamination to the operators sterile gown and defeats the purpose of reducing the bioburden load into sterile areas. These overall design flaws have not been adequately addressed in your response.

Records and Reports

2. Records related to both media fill and batch production were deficient in that they were lacking accurate reproduction and accomplishment of significant steps. For example:

   a. Media fill batch records are deficient in that they lack significant steps in the media fill operation such as: fill line speed, length of fill time, fill volume checks, lyophilization simulation and corresponding process parameters.
   b. Batch production records were incomplete or inaccurate in that employees required to initial various steps of the production record were not doing so at time of performance, mixing times were not being followed, and there was no second person review of critical steps as they occurred.

Your response and translated procedures regarding these deficiencies indicate you completed the corrective action in May 7 and June 30, 1999. However, your response failed to include production and media fill batch records showing correction of the items mentioned on the FD-483. Please provide copies of batch records with the modification which corrected these deficiencies.

Personnel and Environmental Monitoring Controls

3. Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are deficient in that:

   a. The gowning procedures and the corresponding training program have not been shown to be effective.
   b. Personnel were observed practicing inadequate aseptic procedures (techniques).
   c. Failure to adequately monitor the environmental conditions of the class 100 and class 10,000 areas during aseptic operations as follows:
      1. Areas where aseptic connections and partially stoppered vials are exposed.

2. Curtain surfaces along the filling line.
3. All personnel entering the sterile core.
4. Critical surface sampling at the end of filling operations.

d. Incomplete or inadequate investigations when personnel monitoring samples exceed the action limits.

Your response to 4.a., failed to provide documentation of employee training and qualification of gowning technique as reported. Similarly, your response to 4.c., failed to provide environmental records demonstrating monitoring during set-up, tray loading, surface monitoring at end of operations, or assessment of potential risk areas and investigations of action limit excursions for 1999, that support the sterility assessment of the involved batches. Please provide this information.

Lyophilizer Chamber

4. The[ ]lyophilizer chambers are not sterilized after every batch, they are sterilized only after the completion of a product campaign run.

Lyophilizer chambers should be sterilized after each cycle because of the potential for contamination of the internal equipment surfaces by personnel and manipulative activities which increase bioburden and particulate levels. Your response indicate that the chambers will be sterilized before each batch of product intended for the U.S. market according to procedure[ ] Please provide documentation of chamber sterilization prior to batches that were recently sent to the U.S.A. and validation studies demonstrating effective sterilization of the chamber. Also of concern, is the effectiveness of removing from the lyophilizer chamber surface, residues of products (and sanitizing agents if used) after the completion of a product campaign run. If the chamber is not dedicated to a single product line, please demonstrate effectiveness of cleaning with the worst case product line.

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.

Failure to correct these deficiencies may result in FDA denying entry of articles manufactured by your firm into the United States. The articles could be subject to refusal of admission pursuant to Section 801(a)(3) of the Act in that the methods and controls used in their manufacture do not appear to conform to Current Good Manufacturing Practices within the meaning of Section 501 (a)(2)(b) of the Act.

Please respond to this letter within 30 days of receipt. Your response should include data collected in your correction to the deficiencies cited as well as copies of procedures not already included. Specific time frames for correction and commitments with follow up documentation should also be supplied or reported as forthcoming. Attach English translations of supporting documents. Please identify your response with CFN 9610259. Until FDA can confirm compliance with CGMP's and correction to the deficiencies, this office will recommend disapproval of any new applications listing your firm as a manufacturer of aseptically sterilized small volume parenteral 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