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

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WARNING LETTER

MAY 28 1999

FEDERAL EXPRESS

WL No. 320-99-03

Antonio Ilardi, Ph.D.
Manufacturing Operations Director
Eli Lilly Italia S.p.A.
Via Gramsci, 731
50019 Sesto Fiorentino, Italy

Dear Dr. Ilardi:

The U.S. Food and Drug Administration has completed its review of the recent inspection of your sterile pharmaceutical manufacturing facility in Sesto Fiorentino, Italy by Investigators David C. Pulham and Victor J. Gangi during the period of February 1 - 5, 1999. The inspection revealed significant deviations from current good manufacturing practices (CGMP) in the manufacture of sterile pharmaceuticals. The deviations were presented on an FDA 483, List of Observations, 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.

The following are among the most significant CGMP deviations noted during the inspection:

1. The aseptic processing areas are not designed and operated to prevent contamination of sterile product, components and surfaces. For example:

   a. Exposed sterile products and/or components were not adequately protected from environmental contaminants prior to sealing.

Our inspection noted that there were no barriers [for approximately 10 feet] separating the Class 10,000 area from the Class 100 conveyors between the[ ]and the[ ]Additionally, shrouds between the Class 10,000 and Class 100 areas around the filling machine are cut away creating disruption of the unidirectional airflow at working heights.

   b. Filling line vacuum hoses were not sterilized.

   c. There was a lack of unidirectional airflow (UAF) over sterile products and components in critical Class 100 areas.

For example, smoke studies do not demonstrate unidirectional airflow over sterile vials from the [ ] to the [ ] where the [ ] connection is made during setup, and next to the sterile vials turn table. Additionally, the flat surface on top of the filling machine directly above the open sterile drug [ ] causes air turbulence in adjoining areas.

Your 2/25/99 written response to the FDA 483 indicates that you will work to improve the UAF over the small section of the [ ] Please provide us with a description or plan of how you intend to accomplish the improvement of the UAF.

d. Critical surfaces for the aseptic core are not maintained in a Class 100 environment between equipment sterilization and filling operations.

Our inspection noted that there is no assurance that critical surfaces in the aseptic core, such as, the [ ] are maintained under a Class 100 environment between sterilization of the equipment and filling operations. These pieces of equipment are placed in cloth bags, autoclaved and transported through Class 10,000 areas to the aseptic core. There is insufficient data to support if these cloth bags are designed to maintain sterility.

While your written response to the FDA 483 indicates that this practice will be reviewed, your firm did not provide details specifically addressing what the review will entail. Additionally, your response failed to describe how revalidation will be accomplished. Please provide us with the results of your review and the revalidation of the bag closures.

2. Media fill procedures were inadequate in demonstrating that the commercial process is capable of consistently producing sterile units. For example:

   a. They do not adequately simulate the aseptic processing operations.

For example, media fills have included [ ] aseptic bag change per shift. However, normal production includes the changing of [ ] aseptic bags per lot in a [ ] hour time frame.

Your response indicates that [ ] aseptic bags per shift will be changed during media fill operations. This response does not address the total number of bags to be changed in the [ ] hour period. Media fills should simulate normal and worst-case operations.

   b. Interventions were not documented.
   c. Media fills have been invalidated due to contamination during "difficult aseptic connections" although documentation did not support any problems.

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. Until the FDA has confirmed that your firm is in compliance, we will not recommend approval of any applications listing your facility as a supplier of sterile pharmaceutical products.

Your 2/25/99 written response to the FDA 483 is deficient in that it failed to address the FDA 483 issues in a global manner. You must assure that similar problems are not occurring in other areas of your plant. We strongly 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 be advised that failure to adequately correct the aforementioned deficiencies could potentially result in your products being denied entry into the United States. These articles may be refused admission as stated in Section 801(a)(3) of the Federal Food, Drug & Cosmetic Act, in that the methods and controls used in their manufacture do not appear to conform to current good manufacturing practice within the meaning of Section 501(a)(2)(B) of the Act.

Please contact Compliance Officer Alicia M. Mozzachio [telephone: (301) 594-0095; fax: (301) 594-2202] of this division at the above address if you have any questions. Within your written response to this letter, detail corrective actions you plan to take or have taken to bring your operations into compliance. Please include an updated timetable of when each of the corrections will be completed and attach English translations of supporting documents. Please reference CFN# 9611152 within your written response. We request that you respond in writing to this warning letter within 30 days of receipt.

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: Director, Division of Emergency and Investigational Operations Branch, HFC-134, 5600 Fisher's Lane, Rockville, MD 20857. You can also contact that office by telephone at (301) 443-1855 or by fax at (301) 443-6919.

Sincerely.

Joseph C. Famulare
Director
Division of Manufacturing and
Product Quality, HFD-320

cc:

Mr. Sidney Taurel, CEO and Chairman of the Board
Lilly Corporate Center
Indianapolis, Indiana 46285