DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Detroit District
1560 East Jefferson Avenue
Detroit, MI 48207-3179
Telephone: 313-226-6260

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WARNING LETTER
2001-DT-12

March 2, 2001

Sidney Taurel
Chief Executive Officer
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

Dear Mr. Taurel:

Investigators Thomas Arista, Patricia Cochran and Jeffrey Sommers conducted an inspection of your firm's aseptic drug manufacturing operations at Building [redacted] in the Indianapolis, Indiana campus from January 29 to February 23, 2001. Our Investigators documented serious deviations from the Current Good Manufacturing Practice (CGMP) regulations (Title 21, Code of Federal Regulations, Parts 210 and 211), which cause your drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food Drug and Cosmetic Act. While examples follow, you should refer to the FD 483, List of Inspectional Observations, which was issued at the conclusion of the inspection (copy enclosed) for additional details.

1. Failure to have a Quality Control Unit adequate to perform its functions and responsibilities as demonstrated by the number and types of inspectional observations. [21CFR211.22]
2. Failure to assure that all media filled bottles are incubated or incubated for the required period of time and temperature. [21CFR 211.100]
3. Failure to establish appropriate written procedures designed to prevent microbial contamination in drug products purporting to be sterile. [21CFR 211.113(b)]

For example,

(A). The incubation temperature for media filled vials used in the Environmental Monitoring Program is not justified with data per the SOP for "Use of Media Fills for Parenteral Product Aseptic Processing Validation."

(B). There is no written procedure that describes an evaluation process in order to verify and confirm the integrity of HEPA filters in the depyrogenation tunnel's hot zone.
(C). There is no procedure for the set up of stoppering machines used during the production of aseptically filled products.

4. Failure to demonstrate the adequacy of the facility as it relates to flow of air, people, and product.

For example,

A). Smoke studies did not conclusively show that there is an appropriate flow of air and control conditions in order to assure that the opened or partially stoppered vials are not compromised during the aseptic filling process. [21CFR 211.160]
B). The facility design does not preclude cross contamination by exposed employee flow in the event of a spill in the lyophilization area. [21CFR 211.42(c)(5)]
C). There is not a clear delineation of Class 10,000 and Class 100,000 areas in room 234, which is used for solution preparation. [21CFR 211.42 (c)(5)]
D). The partially stoppered vials are not kept in a class 100 environment during mobile cart transfer process to the lyophilizer. [21CFR 211.42(b)]

5. Failure to appropriately validate equipment.

For example,

A). The [redacted] isolators. [21 CFR 211.160]
B). Failure to document the rationale behind established alarm times to monitor the specified differential air pressures within the manufacturing areas. [21 CFR 211.68]

The above list of deviations is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure adherence to each requirement of the Good Manufacturing Practice Regulations. Other Federal agencies are advised of the issuance of all Warning Letters about drugs so that they may take this information into account when considering the award of contracts. Additionally, pending NDA, ANDA or export approval requests may not be approved until the above violations are corrected.

We request that you take prompt action to correct these deviations and to ensure that your drug manufacturing systems are in full compliance with the

Act and regulations promulgated thereunder. Failure to make prompt corrections may result in regulatory action without further notice, such as seizure and /or injunction.

We realize that Eli Lilly Company has multiple locations. This letter is an official notification that FDA expects all of your locations to be in compliance. We recommend that all of your locations be evaluated and that corrective action be taken corporate-wide if deficiencies are found.

We acknowledge receipt of a number of draft documents generated during the inspection to effect correction. We also understand that your firm will have a written response to the FD 483 to Detroit District by March 7, 2001. We will meet with representatives of your firm as requested by [redacted] Director, Corporate Quality Assurance on March 15, 2001.

Please notify this office in writing within fifteen (15) working days of receipt of this letter, of any additional steps you have taken to correct the noted violations including an explanation of each step being taken to prevent the recurrence of similar violations. If additional corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which corrections will be completed.

Any additional correspondence should be directed to the Food and Drug Administration, attention Mrs. Judith A. Putz, Compliance Officer at the above address.

Sincerely yours,

Raymond V. Miecko
District Director
Detroit District

Enclosures: FDA 483 dtd. February 23, 2001

cc via certified mail:

[redacted]
Building [redacted]
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285