DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration
New England District

One Montvale Avenue
Stoneham, Massachusetts 02180
(781) 596-7700
FAX: (781) 596-7896

WARNING LETTER

NWE-08-09W

VIA FACSIMILE & CERTIFIED MAIL

February 27, 2009

Mr. Henri Termeer
Chairman, President and CEO
Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142

Mr. Termeer:

The Food and Drug Administration (FDA) conducted an inspection of Genzyme Allston Landing Facility, located at 500 Soldiers Field Road in Allston, MA, from September 15 – October 10, 2008. During the inspection the FDA investigators documented significant deviations from current good manufacturing practice (CGMP) in the manufacture of licensed therapeutic drug products, bulk drug substances, and drug components. These products include Fabrazyme®, Cerezyme®, and Myozyme®. These deviations from CGMP include non-compliance with section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (FD&C Act), the requirements of your biologics license application approved under 351 of the Public Health Service Act (PHS Act), and Title 21, Code of Federal Regulations (21 CFR) Parts 210 and 211.

At the close of the inspection the investigators issued a form FDA 483, Inspectional Observations, which describe a number of significant objectionable conditions relating to your firm's compliance with CGMP. Significant deviations observed during the inspection include, but are not limited to, the following:

CGMP DEFICIENCIES CONCERNING DRUG PRODUCTS

1. Failure to establish and follow written procedures designed to prevent microbiological contamination of drug products purporting to be sterile [21 CFR § 211.113(b)]. For example:

    a. Air flow pattern testing studies, executed in August of 2007 during the operational qualification of the HVAC system for fill suite FF2-16, do not fully demonstrate air flow

movement away from work surfaces during representative personnel activities and manual simulations of the aseptic filling processes. For example the following operations and practices were not preformed during air flow pattern testing studies:

1. Critical aseptic connections
2. Routine functions of aseptic core operators, for example:
   - Manually placing stoppers or reorienting stoppers using forceps for filled vials
   - Withdrawing unfilled vials from the filling line for weight checks
   - Redirecting filled vials typically with stoppers on the exit feed wheel
3. Unidirectional air flow over the rotary in-feed table
4. Opening the lyophilizer door or the automated double doors into the aseptic preparation area
5. Active viable air sampling

b. The aseptic filling of drug products on the (b) (4) filling line at the speed of (b) (4) has not been validated.

CGMP DEFICIENCIES CONCERNING BULK DRUG SUBSTANCES AND DRUG COMPONENTS

In addition, the inspection covered active pharmaceutical ingredients and significant deviations in the manufacture of your bulk drug substance and drug components were observed during the inspection. These deviations cause your bulk drug substances and drug components to be adulterated within the meaning of Section 501(a)(2)(B) of the FD&C Act. Specific areas of concern include, but are not limited to, the following:

Production and Process Controls

2. You failed to assure that there are written production and process controls designed to assure that the drug has the identity, strength, quality, and purity they purport or are represented to possess. For example:

   a. Your firm does not conduct adequate monitoring of bioburden after hold times of intermediates or pooled buffers during purification of Fabrazyme®, Myozyme®, and Cerezyme®.

   b. Pooled buffers used in purification steps are not adequately controlled for composition. Specifically, the current procedural and automated in-process controls for formulating pooled buffers do not assure that the pooled buffers will meet their specifications.

Your follow up to these documented deviations did not include training of operators or those supervising formulation operations.

Maintenance of Equipment

3. Written procedures are not followed for the maintenance of equipment used in the manufacture, processing, packaging or holding of drug substances. For example:

   a. Internal surfaces and manual valves on the stainless steel chromatography columns used during drug substance purification are not adequately maintained. Maintenance has never been performed on the interior of columns to prevent adverse impact on cell cultures due to metal contamination. Visible rouging was observed on the exterior of the chromatography skid (b) (4) used in purification of Myozyme®.

   b. For the Cryoshippers which are used to transport master cell banks and working cell banks between manufacturing facilities: (1) The use of these cryoshippers has not been validated, (2) Maintenance has not been performed on any of the (b) shippers in use at the time of the inspection, and (3) The manual for these shippers states that the life expectancy of the shippers is 5 years. (b) (4) of these shippers have been in use since approximately late 2002 or early 2003.

Computerized Systems

4. Your firm failed to maintain computerized systems in a validated state. For example, the (b) (4) console, used for formulation for the elution buffer for Fabrazyme®, has not been updated since 1999. The specific gravity value entered into this system in 1999 is incorrect.

The deficiencies described in this letter are indicative of your quality control unit's failure to fulfill its responsibility to assure the identity, strength, quality, and purity of your drug products and drug substances.

Genzyme's written responses dated October 31, 2008, and February 23, 2009

We have reviewed your written responses dated October 31, 2008, and February 23, 2009, addressing Form FDA 483 issued October 10, 2008, and acknowledge your report of completed and in-progress corrective and preventive actions. Additional details to fully evaluate the adequacy of the corrective actions are needed. Our evaluation of your responses and request for further information follows, and is numbered to correspond to the items listed on the Form FDA 483:

Observation 1

Please provide the protocol(s) for your engineering studies and procedures for your new bioburden monitoring program. Regarding your procedures for collecting data to establish bioburden action limits for purification intermediates and drug substance, please address

- whether the (b) (4) referenced in your October 31, 2008 response are from (b) (4) different production lots.
- the basis for any sampling performed.

- the basis upon which appropriate action limits will be established, particularly with regard to infrequently manufactured products.

Please provide an update on the bioburden monitoring programs described in your responses.

Also, please explain your procedures for tracking the length of time that intermediates, drug substance, and buffers have been held.

Observation 2

Please provide the protocol(s) or procedure(s) for collecting data to establish bioburden action limits for pooled buffers. Also, please address

- whether the (b) (4) referenced in your October 31, 2008 response are from (b) (4) different production lots.
- the basis for any sampling performed.
- the basis upon which appropriate action limits will be established, particularly with regard to infrequently manufactured products.

Please provide an update on the bioburden monitoring programs described in your responses.

Please provide an update on the initial evaluation of buffer composition and provide the protocol(s) for the follow up studies referred to in your February 23, 2009 response.

Please provide a summary of the "technical evaluation of the in-process controls tests used to confirm buffer formulation" to which you committed to conduct in your October 31, 2008 written response.

Please address re-training of the operators formulating buffers and those supervising these operations. Our inspection noted that your firm documented deviations in the formulation of pooled buffers, but failed to conduct re-training as follow-up to the deviations to prevent their recurrence.

Observation 6

Your February 23, 2009 response indicates that you have completed your proposed corrective actions with respect to Observation 6, which included an additional air flow pattern study to qualify the HVAC system for fill suite FF2-16. Please indicate if your firm continued aseptic filling operations in fill suite FF2-16 prior to completing this air flow pattern study. If you continued filling operations please provide your justification and evaluation of product impact. In addition, please provide the final report from the air flow pattern study.

Observation 4B, 7, & 11

Your October 31, 2008 response indicates your firm continues to operate the (b) (4) aseptic fill line at speeds up to (b) (4) prior to validating the operation. Please provide your justification and evaluation of product impact.

Please clarify when your firm intends to validate the aseptic filling line. In response to FDA 483 Observation 7, you committed to execute validation of the fill line speed in December 2008. However, in response to FDA 483 Observation 11, you committed to validating the fill line speed in the third quarter of 2009. It is not clear when you will validate the aseptic fill line. Please provide specific details and documentation of your proposed action.

Observation 9

Please indicate if the chromatography column in question remains in use, if it has been evaluated or if maintenance has been performed. If the column is or will remain in use, please provide your justification, including evaluation of the column and any maintenance performed, and an evaluation of product impact.

Observation 10

We acknowledge your commitment not to use the cryoshippers prior to execution of validation for transport of cell banks between the Framingham, MA and Allston, MA facilities. However, these cryoshippers are also used to transfer cell banks from Framingham, MA to San Diego, CA and to Belgium. Please indicate whether you have also ceased using the cryoshippers for cell bank shipments to San Diego, CA, and Belgium until the validation is completed. If not, please provide a justification.

Observation 15

We acknowledge your commitment to identify inconsistencies between the (b) (4) automated system and the production records regarding specific gravity values for buffers your firm manufactures (e.g. Fabrazyme Elution Buffer).

The inspection team noted that this automated system, containing formulas and recipes for buffers was programmed in 1999 and has not been reviewed or updated. We are concerned that other discrepancies in other values may exist. Please comment on how you will assure all values programmed into the (b) (4) automated system, and other automated systems, are consistent with current master batch records.

Neither this letter nor the observations noted on the Form FDA 483, which were discussed with you at the conclusion of the inspection, are intended to be an all-inclusive list of deficiencies that may exist at your facility. It is your responsibility as management to assure that your establishment is in compliance with the provisions of the FD&C Act, PHS Act, all applicable federal laws and regulations, and the standards in your license. Federal agencies are advised of the issuance of all Warning Letters about biological products so that they may take this information into account when considering the award of contracts.

Please notify this office in writing, within 15 working days of the receipt of this letter, of any steps you have taken or will take to correct the noted violations and to prevent their recurrence. Include any documentation necessary to show that correction has been achieved. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed. Failure to promptly correct these deviations

may result in further regulatory action without further notice. Such actions may include license suspension and/or revocation, seizure or injunction.

Additionally, FDA may withhold approval of requests for export certificates, or approval of pending new drug applications listing your facility as a manufacturer until the above violations are corrected. A re-inspection may be necessary.

If you no longer manufacture or market any of your drug products, your response should so indicate, including the reasons for, and the date on which, you ceased production.

Please direct your response or any questions you may have to Amber Wardwell, Compliance officer, Food and Drug Administration, One Montvale Avenue, 4th Floor, Stoneham, Massachusetts 02180. Her telephone number is (781) 596-7823.

Sincerely yours,

John R. Marzilli
District Director
New England District