DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
1 Montvale Ave Stoneham, MA 02180 781-596-7737	9/15/08-10/10/08
	FEI NUMBER 1000305672

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Kathleen Retterson, Vice President

FIRM NAME	STREET ADDRESS
Genzyme Corporation	500 Soldiers Field Road
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Allston, MA 02134	Drug Manufacturer

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS; AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

1. Bioburden is not adequately monitored during the purification of Myozyme 2000 L process, Cerezyme, Fabrazyme and Myozyme 160 L process.

2. Buffers are not adequately controlled for composition nor monitored for bioburden.

3. The batch production record for drug substance is not adequately controlled.
   - For example, the production record is printed on green paper and is issued by Quality Assurance. Attached to the production record are white manufacturing records. Operators frequently record the performance of manufacturing activities, test results or meter readings in the manufacturing records. The manufacturing records are not issued by Quality Assurance. There is no method to control the production of manufacturing records or to account for manufacturing records.

4. A. Activities performed during drug substance manufacture are not adequately documented. For example:
   - When performance of an activity is optional at a given time point (b) (4) (b) (4) there is frequently no place in the batch record to record whether the activity was performed.
   - Dated and signed crossing-out of optional activities that are not performed is not used consistently in the batch record.
   - Additional activities may be performed during manufacture of some commercial batches as part of a study. These activities are not always reflected in the batch record.
   - Data are recorded in incorrect units.

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	Debra Emerson	Debra Emerson, Investigator	10/10/2008

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B. Activities performed during drug product manufacture are not documented. For example:

a. Myozyme (b) (4) was filled into vials on 9/16/08. The filling batch record does not include the number of vials that were not stoppered by the automated (b) (4) stoppering machine and stoppered manually by operators prior to lyophilization.

b. The forceps used to stopper the vials are not listed in the production record.

5. Activities are performed during drug substance manufacture that are not authorized by QA.

- During fermentation of Fabrazyme the (b) (4) to try to (b) (4) Although the adjustments were within the approved range the study was not appropriately documented.

6. (b) (4) studies executed August 2007 during the operational qualification of the HVAC system for fill suite FF2-16, did not demonstrate the following:

- Critical aseptic connections
- Routine functions of aseptic core operators, for example:
  a. manually placing stoppers or reorienting stoppers using forceps for filled vials
  b. withdrawing unfilled vials from the filling line for weight checks
  c. redirecting filled vials typically with stoppers on the exit feed wheel
- Unidirectional air flow surrounding the rotary in-feed table
- Opening the lyophilizer door or the automated double doors, as typically operated, into the aseptic preparation area and the effects on unidirectional airflow
- Active viable air sampling and the effects on unidirectional airflow

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7. The aseptic filling of all drug products into vials at higher speeds on the (b) (4) filling line has not been adequately qualified for its current use. The (b) (4) filling line is currently run at (b) (4) per minute for the 20ml vials. The data reported in validation studies documents that above (b) (4) per minute, the stoppers clog in the stoppering machine and performance of the machine is affected.

8. The procedure "Surface Monitoring (b) (4) " QC-019-02, version 03/11/2008 does not require personnel exiting the aseptic fill suite to (b) (4) on the (b) (4) (b) (4) this procedure (b) (4) Additionally, personnel monitoring observed on September 16, 2008 exhibited (b) (4) (b) (4)

9. On 9/17/08 rouging was seen on the outside of the chromatography column. Internal surfaces and manual valves on the stainless steel chromatography columns used during drug substance purification are not adequately maintained in that they have never been maintained. In January 2008 the facilities chromatography skid maintenance SOP was updated with instructions for such maintenance. Performance of this maintenance is dependent on manufacturing requesting the maintenance. There is no procedure in manufacturing instructing them to notify facilities that maintenance is needed.

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10. For the Cryoshippers which are used to transport master cell banks and working cell banks between manufacturing facilities:

- The use of these cryoshippers has not been validated.
- The manual for these shippers lists preventative maintenance steps for both continuous maintenance and annual maintenance. The firm has not conducted any maintenance on any of (b)(4) (4) shippers currently in use.
- 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 2002/2003.

11. Quality assurance reviewed and approved a final validation report for The Use of Bagged Serum Stoppers in Liquid Fill Finish Processes in the Fill/Finish Area at Allston Landing, study (b)(4) ....., which did not meet the protocol requirements.

12. The firms overall assessment of the cleaning validation of Myozyme and Fabrazyme for (b)(4) .....was inadequate as the (b)(4) to determine which product is the most difficult to remove was unknown until September 5, 2008.

13. The procedure entitled: Document System and Control, GN-001-01, is used for the review and approval of documents. This procedure was not followed in the approval of all documents.

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14. Deviation files are incomplete. For example:

- For those deviations resulting from operator error, the deviation file did not contain documentation that the operators were re-trained or counseled as a corrective measure.
- For deviations where informal investigations were conducted, there was no documentation of the investigation.

15. Portions of formulating the Fabrazyme Elution Buffer are automated. The formulation for the Elution buffer was entered into the (b) (4) console which is an automated system. Since 1999, the specific gravity for the buffer was incorrectly entered into the computer program as (b) (4) The correct specific gravity of the Fabrazyme Elution Buffer is (b) (4) as indicated in the current production record.

16. A. Master production and control records for drug product are deficient in that they:

- Do not include a description of the drug product containers, closures and packaging materials, a specimen or copy of each label and all other labeling, and the signatures and dates entered by the person or persons responsible for the approval of labeling.

B. Master production and control records for drug substance are deficient in that they:

- Do not include an accurate statement of weight of each component
- Do not include a statement of theoretical yield including the maximum and minimum percentages of theoretical yield beyond which investigation is required.

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DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

Debra Emerson, Investigator

Megan Haggerty, Investigator

Kent Conforti, Investigator

Susan Kirshner, Specialist

Jack Ragheb, Specialist

Marilyn Welschenbach, Assoc. Director

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