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 781-596-7700	10/8/09 - 11/13/09
	FEI NUMBER 1000305672

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Henri A. Termeer, Chairman, President, and CEO

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

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

1. The Vice President of Quality Operations US Therapeutics confirms there is no established standard operating procedure to describe the periodic review, and the contents of the review, of deviations and investigations performed by the Quality Unit. The Quality Unit performs individual reviews and approval. However, there is no overall assessment of the deviations and investigations with respect to their impact on the manufacturing operations and Quality Controls to prevent their reoccurrence.

• For example, the firm has received many Product Event Intake Reports for the presence of particles in the finished drug product. In the investigation into the source of the particles in the drug product has found the following types of particles: metal particulates, colored and transparent fibers (cotton and polyester), rubber like particles, and glass particles. The firm has not completely identified the source of all foreign matter contaminants or implemented corrective measures to reduce the foreign matter in final drug product.

2. There is a failure to thoroughly review the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed. Specifically,

a. Investigations into metal particle contamination in finished drug product concluded equipment used in the aseptic fill process sheds metal particulates into vials before drug product is filled based on the equipment design and intended use. The equipment is used for filling of Myozyme, Fabrazyme, Cerezyme, and Thyrogen. Your follow up to this conclusion is inadequate because it fails to address prevention contamination before long term corrective actions are implemented in 2010 and 2011.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	Debra M. Emerson	Thomas J. Arista, Investigator Debra Emerson, Investigator	11/13/2009

Dennis Gallagher
Richard Ledwidge
Timothy Hallagher

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b. Investigations into particulate matter in finished drug product failed to identify corrective actions for deficiencies noted in your firm's visual inspection process using the (b) (4) at a rate of (b) (4) vials (b) (4). For example, investigation noted differences between your inspection method and the method used by Genzyme Japan which include pacing, light source, the distance of examination and that particles found by the secondary inspection were approximately (b) (4) than those detected using your current method. On multiple occasions, foreign matter has been found during Genzyme Japan's visual inspection of finished drug product which has been previously visually inspected and released by your firm.

3. Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design to facilitate operations for its intended use. Specifically,

• Your firm is using vial pans used in the depyrogenation process of drug product vials which you have identified as a source of metal particle contamination in finished drug product because of metal-on-metal contact with the trays and prep components such a metal base, lid, or ring.

• Your firm upgraded the refrigeration skid which is used to run the lyophilizer in January 2003. This included the replacement of equipment and computer upgrades. There are (b) (4) lyophilizer. The Operational Qualification performed on the system did not include functional tests for all critical steps. There was an error in one of the bits for compressor (b) (4) This bit was entered as (b) (4) start compressor #1 condenser cooling (b) (4) and the bit should have been entered as (b) (4) Due to this error, there was an issue on 5/15/07 during the lyophilizer cycle for Cerezyme lot A7034 which did not allow the compressor to cycle off and required manual intervention.

• The (b) (4) filling line has been in place and in use since 1994. The (b) (4) filling line has not been calibrated for line speed, stopper bowl speed, or volumetric control.

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4. Control procedures are not established which monitor the output or validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Specifically,

• Validation of the fill process for low volume products is inadequate in that full size validation runs have not been executed since process and equipment parameter changes have been implemented to prevent low fill volumes.

• The 100% visual inspection conducted by your firm on all finished drug products is cannot reliably detect and reject vials containing foreign matter including, but not limited to metal particles. For example, on multiple occasions released drug product has been rejected and returned after a second 100% inspection, conducted by a consignee. Your investigation noted differences in the inspection methods including pacing, light source, the distance of examination and that particles found by the secondary inspection were approximately (b) (4) (b) (4) than those detected using you current method. (b) (4)

• The (b) (4) fill height visual inspection conducted on 100% of finished product is cannot reliably assure out of specification low volume drug products are rejected. Your firm concluded that the inspection can only reliably detect fill volumes (b) (4) volume products such as Fabrazyme 5mg and Thyrogen. Furthermore, your firm concluded the inspection is capable of detecting a fill height difference of (b) (4) but a difference of (b) (4) falls outside the potency range for low volume products.

5. Routine calibration of mechanical and electronic equipment is not performed according to a written program designed to assure proper performance.
• Specifically, a written program has not been established for calibration of the proper performance of the (b) (4) fill equipment. The (b) (4) fill equipment has been in place and in use since 1994 and used for filling of drug products including, Myozyme, Fabrazyme, Cerezyme, and Thyrogen. The equipment has not been calibrated for fill volume or speed.

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6. No appropriate investigation was conducted when a returned drug product appeared to implicate associated batches of drug products. Specifically,

• Investigations are inadequate in that they do into include evaluation of all pertinent data collectively. For example lot A9013 Cerezyme (b) (4) units per vial underwent 100% inspection prior to release with (b) (4) vials rejected for foreign matter and (b) (4) vials released by your Quality department this rate did not exceed your internal alert limit. A total of (b) (4) of these released vials underwent a second 100% inspection and (b) (4) vials were rejected for foreign matter, which equates to a reject rate of (b) (4) which does exceed your internal alert limit. By combining the rejects from the pre-release 100% inspection and the second 100% inspection the total rejects rises to (b) (4) This doesn't account for the (b) (4) vials released which never underwent a second 100% inspection.

• Investigations into returned drug product are inadequate in that they are limited to investigation of a product specific lot. For example (b) (4) was initiated based on return of Cerezyme (b) (4) units/vial lot A9013 for particulate matter. The investigation was limited to the manufacturing records, testing and inspection records, returns, investigations, etc. relating to only lot A9013. Your firm did not consider, as part of the investigation, other products which have been returned for particulate contamination, or other lots which have been returned for particulate contamination, or the frequency of returns for particulate contamination in any product or lot.

7. The "Certification & Re-certification of the Aseptic Filling Processes at Allston Landing", document VP-026-15, is established, "To provide a procedure for describing the requirements for certifying new aseptic filling processes and re-certifying existing aseptic filling processes." "Not more than one contaminated vial may be detected for a fill to be considered successful." 'If more than one contaminated vial is detected, this is considered an "Action Level", which requires that an investigation be performed, and corrective actions taken before re-initiating the certification process." (Note: this document is applicable for all media fills used to support the aseptic filling process of the Cerezyme (NDA # 020367), Fabrazyme, (BLA #103979) and Myozyme (BLA # 125141) finished products manufactured at the Allston facility).

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CITY, STATE AND ZIP CODE Allston, MA 02134	TYPE OF ESTABLISHMENT INSPECTED Drug Manufacturer

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The following table lists media filled batches used in support of the 2008 & 2009 aseptic filling processes preformed at the Allston Fill/Finish suite. As summarized below not all media filled vials are incubated for the requisite time and temperature, i.e., discarded vials absent an assignable cause for their rejection, which precludes the Quality Unit from confirming that, "The results of the Media Fill Qualification were evaluated to determine if the aseptic process met the criteria stated in the protocol" and from "...certifying new aseptic filling processes and re-certifying existing aseptic filling processes".

Media Fill Study	*Date of Fill*	*Vial size*	*Vials Incubated*	*Number of rejects*	*Assignable cause for rejects*
(b) (4)	(b) (4)		(b) (4)	(b) (4)	*Unknown / unclear*
(b) (4)	(b) (4)		(b) (4)	(b) (4)	*Unknown / unclear*
(b) (4)	(b) (4)		(b) (4)	(b) (4)	*Unknown / unclear*
(b) (4)	(b) (4)		(b) (4)	(b) (4)	*Unknown / unclear*
(b) (4)	(b) (4)		(b) (4)	(b) (4)	*Unknown / unclear*

8. The procedure entitled: Certification and Re-certification of the Aseptic Filling Processes at Allston Landing, VP-026-15, requires operators be involved in a successful media fill to be qualified. Operators are to be re-qualified in a media fill every (b) (4) (b) (4) Operators are to be qualified before they are allowed perform any aseptic filling operations.
   - Operator (b) (4) was in the fill suite during the filling of Cerezyme lot A7034 on 5/15/07 and for Cerezyme lot A7030 on 4/30/07. Operator (b) (4) was in the fill suite during the filling of Cerezyme lot A7030 on 4/30/07. Operators (b) (4) were last qualified during the 1/18/06 media fill.
   - Operators (b) (4) were in the fill suite during the filling of Thyrogen lot A9053 on 9/9/09 and Thyrogen lot A9054 on 9/15/09. Neither operator has been qualified thru a successful media fill.

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9. The "Aseptic Qualification for Personnel to Participate in Filling Operations", document #MF-101-07 establishes a standard practice (b) (4) and "a procedure for the qualification of personnel to enter the Fill Finish Core Area during a filling operation in lieu of initial participation in a media fill operation." And, "due to the timing of these media fills and the hiring of new operators an alternate, more rigorous approach was developed which would serve to qualify operators to participate in sterile operations (non product contact steps) until the next scheduled media fill." Despite the aseptic fill processing commitments submitted in the NDAs and BLAs, the "more rigorous approach" to aseptic media fill qualification of personnel is a "more rigorous scenario than participating in a media fill" in support of the aseptic filling process has not been submitted to the Agency for prior or post approval change to the applications. In addition,

a. The Microbiology Manager confirms there is no document that describes the "more rigorous approach" to qualify operators to participate in sterile operations.

b. There is no record to document or describe how the "more rigorous approach" is comparable or equivalent to, and "more rigorous" than, aseptic media fill operations.

10. There is no record (e.g., batch production and control records) to document the actual number vials that are aseptically filled with microbial growth medium prior to the lyophilization process. In addition,

• The lyophilization process time for routine production, dependent on the finished product, can ranges from (b) (4) or up to (b) (4) The lyophilization process simulation performed during the media fill is approximately (b) (4). The Validation Manager confirms there is no rationale to support the (b) (4) process simulation when compared to a routine lyophilization process time of up to (b) (4)

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11. The Thyrogen® NDA 20-898 commits that the media filled vials are (b) (4) for a minimum of (b) (4) followed by (b) (4) for a minimum of (b) (4) " However, contrary to the NDA media fill incubation commitments the (b) (4) at Allston" document #PR-093-44, establishes and provides specific instruction to "Transfer storage cages to the appropriate Quarantine (b) (4) Area". The storage cages contain the media filled vials and the (b) (4) is performed prior to the requisite time and temperature incubation requirements submitted in the NDA. The NDA does not provide any provision for the (b) (4) of media filled vials prior to incubation. The (b) (4) was performed for all 2008 and the April 1, 2009 media fill re-certifications. (Note: the objectionable condition is applicable for media fills used to support the aseptic filling process of the Cerezyme (NDA # 020367), Fabrazyme, (BLA #103979) and Myozyme (BLA # 125141) finished products manufactured at the Allston facility).

12. The "Certification & Re-certification of the Aseptic Filling Processes at Allston Landing" document #VP-026 -15, lists routine and non-routine interventions for media fill which, "must be incorporated into initial media fill certifications and performed on an (b) (4) bases for media fill re-certifications Non-routine interventions occurring during production fills shall be incorporated into the next schedule media fill." The "Process Validation for Therapeutic Products" document #VP-026-84, establish "Some types of process validation utilize a worst case validation strategy to properly demonstrate process consistency and robustness at commercial scale. During the creation of the process validation protocol, an assessment of operating ranges and worst case conditions is performed when defining the process validation strategy." "The intention of testing at worst case conditions is to ensure the process operates effectively within the allowable batch record range." Despite the aforementioned procedures, the Validation Manager confirmed there is no record to document the rationale that established the routine and non-routine media fill interventions and the frequency of the interventions.

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13. There are aseptic manual connections of the sterile filtered formulated bulk solution transfer hoses from the bulk solution stainless steel vessel to the (b) (4) filling equipment (room FF2-016, ISO-5 / Class 100). The aseptic manual connections are performed under a mezzanine floor (b) (4) located in Filtration Room FF2-09 (ISO-7 / Class 10,000 (b) (4) The aseptic manual connections performed on the formulated bulk solution stainless steel vessel are not made within HEPA filtration to control and prevent the ingress of objectionable microorganisms and non-viable particles. (Note: The objectionable condition is applicable for the Cerezyme (NDA # 020367), Fabrazyme, (BLA #103979) and Myozyme (BLA # 125141) finished products manufactured at the Allston facility).

14. Visual inspection is performed to accept or reject lyophilized finished products for a variety of quality attributes (e.g. cracks, defective closure, improper fill volume, discoloration, cake flaws, and foreign matter on cake, vial, or stopper). The training of operators for the visual inspection process is insufficient in that:

- Operators are qualified for lyophilized product using (b) (4) vials filled with (b) (4), which is not the same consistency or has the same physical characteristics of the lyophilized material. Operators are not qualified using actual lyophilized drug product.
- Operators are not qualified on visual inspection for 5 cc vials. Fabrazyme 5mg and Thyrogen are filled into 5cc vials.
- The visual inspection acceptance and rejection of lyophilized finished product vials is performed by the production department and not by the Quality Unit.

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15. Investigations reviewed were not complete in documentation, investigation, or corrective action. Examples of insufficient investigations are listed below:

• Investigation AIR 1484 dated 4/30/07 which was opened because of a positive result which was obtained from an operator who was (b) (4) sampled per standard procedures from his gloves. The operator was leaving the fill suite after the completion of the filling of Cerezyme A7030. The organism was identified as Bacillus megaterium. The investigation did not confirm the source of the Bacillus megaterium inside the fill suite. The (b) (4) of the fill suite was performed on 6/15/07. There were (b) (4) additional lots of drug product filled in this suite between 4/30/07 and 6/12/07 with no product impact assessment mentioned in the investigation. The investigation did not include confirmation that the (b) (4) removed the Bacillus megaterium from the fill suite.

• Investigation AIR 1517 dated 6/21/07 was opened because (b) (4) HEPA filters in the filling suite failed routine recertification. The investigation found metal particles embedded in several of the HEPA filters. However, no route cause was determined for the source of the metal contamination found in these filters.

• There were multiple investigations opened to document rouging found inside of columns (ex. Purification Columns). The investigations conducted by the firm into the column rouging did not include any analytical testing or assessment as to whether any component of the iron oxide was released into the eluate during processing.

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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 781-596-7700	10/8/09 - 11/13/09
	FEI NUMBER 1000305672

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Henri A. Termeer, Chairman, President, and CEO

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

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16. The documentation recorded by operators in the batch records is insufficient. Specifically,

A. For filling operations:

• Operators do not record which (b) (4) is used during each fill. The firm has (b) (4) different (b) (4).

• Operators do not record the actual knob settings from the (b) (4) filler which includes the speed of the (b) (4) and the setting for the (b) (4) (used to set the line speed).

• Operators do not document the actual number of vials filled during a run. Operators do not document the actual number of vials that are placed into the lyophilizer.

• When an in-process weight check fails during filling, operators are required to notify a supervisor or designee. Page 28 of the Thyrogen filling record provides a place for operators to document this notification. During the filling operations for Thyrogen lot A9054 there was a weight check failure. There was no documentation in the batch record that the operator notified their supervisor. There is also no documentation that quality was made aware of the failed weight check.

B. For inspection operations:

• The procedure entitled: Inspection of Lyophilized Product Using the (b) (4) (b) (4) requires operators "must inspect for no longer than (b) (4) (not exceeding (b) (4)." Inspectors do not document the actual time that they start or stop their visual inspection of vials. Inspectors record the hour in military time and instead of recording the minutes from the clock, they record a calculated percentage.

• The procedure entitled: Inspection of Final Product (unlabeled) Using the (b) (4) (b) (4) at Allston Landing, QA-006-05, requires operators can spend a maximum of (b) (4) consecutive minutes inspecting vials using the (b) (4) The AQL inspection of vials is performed by the quality staff, there is no documentation by these inspectors to record the time that they start or stop their inspection of these vials.

C. For quality investigations:

• In the event that a quality issue detected during filling, the quality department will make the decision that individual trays are to be segregated as they are removed tray by tray from the lyophilizer. This decision made by quality to segregate vials is not documented.

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	Thomas D. Arista, IN Debra Emerson, Investigator	Thomas D. Arista, IN Debra Emerson, Investigator	11/13/2009

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17. The "Decontamination and Restart Plan related to AIR 1871-Rapid Cell Decline related in Cerezyme Bioreactor 5A (Lot #11808406) at the Allston Landing Facility" dated 06/20/09 response to the Vesivirus 2117 contamination, describes that "a more comprehensive and aggressive decontamination strategy needs to be implemented to provide assurance that this viral contaminant has been effectively eliminated." For example,

• The scope of work by for Genzyme, Amendments dated 07/02/09 and 07/07/09 requires (b) (4) (b) (4) studies were conducted in (b) (4) on June 29, 2009 to identify any remediate any potential adverse airflows into or out of the (b) (4)." However, the Associate Director of Quality Control Microbiology, Senior Director of Bulk Manufacturing and the Contractor/Vendor confirm that there are no records to document the (b) (4) studies "to identify and remediate any potential adverse airflows into or out of the (b) (4) area." (Note: the air velocity and flow of air assists to convey the VHP to the hard to reach work surfaces and equipment.)

• (b) (4) will calculate optimal injection duration and placement of the VHP units and fans to achieve optimal VHP concentration and disbursement throughout the target zone." However, there is no record to document the calculations to support the optimal injection duration or a document that describes the rationale to support the placement and locations of the VHP units and fans.

18. The June 23, 2009 VHP Decontamination of Allston Cell Culture (b) (4), describes that "The locations of the BIs are also determined by risk-based approach and a review of the manufacturing process in the area." However, there is no record to document the "risk-based approach and review of the manufacturing process". In addition,

• There is no record to document the locations or placement of the (b) (4) (b) (4) Biological Indicators (BIs) that are used to support the decontamination of the Allston Cell Culture (b) (4) and the bulk manufacturing facility.
• The (b) (4) Bio-decontamination of Allston Landing Facility Bulk Manufacturing Areas in Response to AIR 1871", document #09TRA0165, dated 07/23/09 describes that, "The biological indicators (BIs) were distributed around the target areas in worst case locations". However, there is no record to document the evaluation performed to determine the "worst case locations".

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19. The VHP cycle parameters, e.g., [redacted] (b) (4) [redacted] (b) (4) [redacted] for the various bulk manufacturing areas that include for example the purification process areas, cell culture rooms, media preparation and buffer preparation rooms, are calculated with considerations of the overall room dimensions of the respective target zones with production equipment. However, there is no record to document the manner with which the VHP decontamination cycle parameters were developed. As confirmed by the Contractor/Vendor ((b) (4) [redacted]), the VHP Process was developed via (b) (4) [redacted] (b) (4) [redacted]

20. The July 13, 2009 action notification attachment form documents, "A localized number of BI's are positive after the completion of the VHP of Protein Purification", which was attributed to the BIs being covered with adhesive tape during the VHP decontamination. Despite the strategy described in the June 19, 2009 Decontamination and Restart plan related to the Rapid Cell Decline in Cerezyme Reactor 5A (lot 11808406) at the Allston Landing Facility, VHP decontamination was not performed for the affected areas. In addition,

- Part of the corrective action of the July 13, 2009 action notification, (b) (4) (b) (4) was performed. However, the August 2005 Evaluation of (b) (4) (b) (4) studies document that the (b) (4) "was unable to effectively inactivate the Staphylococcus aureus, Micrococcus luteus and Candida albicans (b) (4) or Bacillus subtilus pores and significantly reduce Bacillus cereus spores".

- The (b) (4) used in the Cell Culture (b) (4) was not included in the WHP decontamination.

21. There is no record to document that the various pieces of equipment used during the aseptic filling process are cleaned and sanitized prior to use (e.g., mobile carts, chairs, step stool) and there is no record to document the cleaning of the production equipment used in bulk manufacturing. In addition,

- There is a metal tool box containing hand tools (e.g., adjustable & hex-head wrenches, pliers, cutters) that are used during the set up of the fill equipment and during routine manufacturing operations for the "aseptic core" and in the aseptic fill room #FF2-016. However, the Production Manager confirms there is no record to document that the tools are steam sterilized or clean and sanitized prior to use or on a periodic basis

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22. The "Evaluation of (b) (4) and Maximum Hold Time to Control Microbial Populations on Hard Surfaces", document #05TRN102 dated 09/07/05 concludes that the (b) (4) was shown to be an partially effective disinfectant by significantly reducing (b) (4) the viability of most gram positive & gram negative vegetative bacteria, yeast and mold spores. However, it was unable to effectively inactivate the Staphylococcus aureus, Micrococcus luteus and Candida albicans (b) (4) or Bacillus subtilus pores and significantly reduce Bacillus cereus spores." In addition,

• The "Sanitization of the Aseptic Area of the Fill/Finish Department at Allston" document #MF-082-50 establishes the frequency for sanitization, which includes a (b) (4) of the Fill/Finish aseptic areas (e.g., FF2-09 & FF2-016) and associated airlocks with (b) (4) (b) (4). However, as previously described the (b) (4) is "unable to effectively inactivate the Staphylococcus aureus, Micrococcus luteus and Candida albicans (b) (4) or Bacillus subtilus pores and significantly reduce Bacillus cereus spores."

23. The "Audit of Aseptic Technique During Filling Operations at Allston", document #QA-100-09" is "used to evaluate the aseptic technique of personnel in fill room FF2-16 for all filling operations including media fills, clinical product fills, and commercial product fills." Quality Assurance personnel observe and evaluate the media fill set-up, aseptic filling and capping operations for compliance to the established procedures. However, a similar level of responsibility, review and approval are not performed for routine production ("commercial product fills"), i.e., routine set-up of the fill room equipment, aseptic filling operations and capping of finished products. In addition,

• A similar level of evaluation is not performed for the filtration steps, (b) (4) performed in room #FF2-09.

24. The design of the aseptic filling room #FF2-016 (b) (4) the ISO-5 areas (Class 100) do not prevent the ingress of objectionable microorganisms and non-viable particles. In addition,

• Due to the design of the aseptic fill room and the (b) (4) filling equipment there are up to (b) (4) production personnel that are needed for the aseptic filling operations, which promotes the ingress of objectionable microorganisms and non-viable particles within the ISO-5 areas.

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25. Due to the design of the building, initial personnel gowning room (b) (4) and the flow of production personnel (b) (4)) within the facility promote the ingress of objectionable microorganisms and non-viable particles into the classified and unclassified manufacturing areas. In addition,
• Production personnel work on or come in direct contact with the large wooden (reception-like) desk that is located in the common personnel corridor, which is not a smooth and cleanable surface. The Associate Director of Quality Control Microbiology and Senior Manager of Fill Finish Operations confirm there is no record to document that the wooden desk is sealed. The Associate Director of Quality Control Microbiology confirms that the wooden desk is not part of EM Program or sampled for the presence or absence of objectionable microorganisms.

26. There is an observation window, approximately (b) (4) that is used to observe the aseptic filling operations. The window seals and the sections where the window stainless steel frame meets, as confirmed by the Director of Quality, Production Supervisor, and Validation Manager, are not sealed such that (b) (4) verified leak" around the window stainless steel molding. The Senior Director Facilities confirms that there is no record to document that the interior surfaces of the wall are sealed. In addition,
• The Quality Assurance personnel observe the media fill set-up, aseptic media fills and the capping operations via the observation window in the personnel corridor. However, not all of the production activities can be observed in that the area where the "reverse weight check" is performed is not visible from the observation window.

27. Production personnel are required to remove their street attire and shoes and don the plant uniform (blue color scrubs and dedicated factory shoes) prior to proceeding to their respective work areas. Dependent on their work area, e.g., filtration room, component preparation, and aseptic filling, production personnel are also required to don additional gowning attire, e.g., lab coat, beard and bouffant hair cover, protective eye wear. However, the production personnel in their blue scrubs plant uniform come in direct contact, via the common personnel corridors and stairwells, with non-production personnel (i.e., personnel wearing their street attire). The production personnel flow and their direct contact with non-production personnel promote cross contamination of microbial and non-viable particles.

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28. The "Guidelines for the Performance of Airflow Pattern Testing for Clean Rooms and Laminar Flow Hoods", document #VP-009-33 "provides minimum guidelines for performing airflow pattern testing ((b) (4) used to assess unidirectional air flow conditions in aseptic processing areas, support cGMP operations at Genzyme's Allston Landing and Framingham facilities." The Senior Director of Quality Operations confirms that the airflow pattern testing and requirements established in the document are a "must". The January 2009 (b) (4) evaluation video does not completely and adequately demonstrate unidirectional air flow within the ISO-5 (Class 100) aseptic fill zones and within the various ISO-5 areas in FF-2-016 e.g., personnel entering and exiting out of the (b) (4) , personnel (b) (4) the filled vials from the tray loader (b) (4) from the stainless steel (b) (4) (b) (4) .
(Note: This is not intended to be an all inclusive list of events). In addition,

• There are multiple HEPA filters in the ISO-5 (Class 100) area i.e., above the (b) (4) equipment that provides a vertical flow of air and a HEPA filter that provides horizontal air flow beneath the (b) (4) equipment and the location where the depyrogenated and siliconized stoppers are off loaded from the (b) (4) into the (b) (4) stopper transfer vessel. The April 2006 (b) (4) study documents the airflow beneath the (b) (4) moving in an upward direction rather than in a downward and outward direction. No evaluation has been performed to determine cause or impact to the sterilized and depyrogenated stoppers of the upward movement of the HEPA filtered air.
• There is an air exhaust vent immediately beneath a HEPA filter that is located on the left hand upper side of the ISO-5 area above (b) (4) The (b) (4) documents HEPA filtered air exiting out of the HEPA filter and directly into the air exhaust vent. The (b) (4) study does not completely or adequately demonstrate unidirectional airflow on the left hand side of the (b) (4) equipment and when personnel are performing the (b) (4) during the (b) (4) from the (b) (4) into the (b) (4) (b) (4)
• The "Certification of HEPA Filters, Biological Safety Cabinets and Chemical Fume Hoods", document #GN-010-36 establishes that "A Metrology representative will also witness (b) (4) Pattern Analysis / Testing for critical Class 100 Bio Safety Cabinets and Laminar Flow Hoods / devices." However, the Metrology Manager confirmed there is no data (i.e., (b) (4) pattern video) to support the (b) (4) Pattern Analysis".

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• The "Operational Qualification Protocol for the Airflow Pattern Testing in the Class 100 (ISO5) Filling Room FF2-16 Located at the Allston Landing Facility" document #04-2534, dated December 22, 2008" provides the "objective of this protocol is to define the requirements and acceptance criteria for the performance of the Operational Qualification of the airflow pattern testing in fill room FF2-16 at Allston Landing. This protocol is in response to corrective actions/preventative action (CAPA) (b) (4) "Successful completion of this protocol will also demonstrate that airflow patterns are adequately tested for turbulence that would interfere with the sweeping action of the air during representative manufacturing operations." The Associate Director of Quality Control Microbiology confirms that the video of the airflow patterns have been reviewed and approved by the Quality Control department. However, there is no record to document the airflow pattern evaluation performed by the Quality Control department to support that the established acceptance criteria was achieved. [Note: the Microbiology Department is responsible for the Environmental Monitoring (EM) Program of the entire manufacturing operations at the Allston facility].

29. There are laminar flow hoods [LAF ISO-5 (Class 100)] that are used during various aseptic operations in bulk manufacturing. Airflow pattern studies have been performed as previously described in the preceding observation. Similar to the ISO-5 manufacturing areas in the Fill & Finish manufacturing areas, the (b) (4) do not completely or adequately demonstrate unidirectional airflow during the various aseptic processing steps performed in the laminar flow hoods. In addition,

• The April 27, 2009 Risk Assessment of the ISO Class 5 Laminar Flow Hoods or ISO 5 Areas to determine those that should be considered as "critical" operation" identified high, medium and low risk categories. The airflow pattern studies for the high risk ISO-5 LAF and biological safety cabinets (BSC) have been evaluated. However, the airflow pattern evaluations have not been performed for the BSCs that are used for the bioreactor sample processing.

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30. There is no record to document the rationale (e.g., evaluation performed to determine and support the justification) for the EM microbial sampling locations, which is ultimately used to support the presence or absence of objectionable microorganisms in the Allston manufacturing facility that includes but is not limited to the ISO-7 (Class 10K) filtration room #FF 2-09 and ISO-5 (Class 100) aseptic filling room #FF2-016 as well as the bulk manufacturing areas. In addition,

- The microbial alert and action levels, that is, the level of microbial contamination that initiate or trigger whether an evaluation is required to determine the cause for the microbial excursions, for the bulk manufacturing facility and the Fill/Finish manufacturing areas are not based on the historical EM sampling data.

31. The 2008 and 2009 (b) (4) EM Trend data document the percent of microbial identification for Gram Positive rods (i.e., spore former, non-spore former, and unknown spore formers) from the EM sampling for the Allston facility, for example;

	2008	2008	2008	2008	2009	2009
Area	(b) (4)					
Fill / Finish	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Bulk mfr.	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

The EM sampling identifies the locations where the microbial contaminants were recovered. However, the evaluations fail to identify the source(s) of the microbial contaminants, for example the root cause for the recurrent presence of the Bacillus species contamination. The root cause evaluation(s) in turn assist to address, and ultimately control, the ingress of objectionable microorganisms.

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

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32. There is a June 16, 2005 '(b) (4) ' that describes the Non-viable Particle (NVP) should be placed (b) (4) above the aseptic filling work surfaces. However, the NVP that is nearest the aseptic fill nozzles, measured by Production Staff, is (b) (4) above the work surface. In addition,

    - There are (b) (4) NVP monitoring probes located approximately 7 feet above the floor on the left hand side of the (b) (4) Lyophilizer and near the glass vial in-feed table in the aseptic filling room #FF2-016. There is no record to document the rationale for the NVPs located on the walls.

33. Non-viable particle measurements are not taken during the routine dynamic operations performed in the Filtration Room #FF-2-09 (ISO-7). In addition,

    a. The NVP measurements are not taken near or next to the area where the aseptic connections of the filtration apparatus are performed. Rather, the NVP are taken approximately in the middle of the room.

34. There is a small step stool used by production personnel when setting up the filling hoses, connections and filling nozzles to the (b) (4) filling equipment. During the set up the personnel position the step stool next to the fill equipment and the shoe covers come within close proximity (approximately 1½- 2') to the filling equipment and fill zones. However, the step stool is not sampled during the EM to determine the presence or absence of objectionable microorganisms.

35. We observed visible particles inside the air return duct from the observation window in front of aseptic fill room #FF2-016. The Quality Unit could not confirm whether the visible particles were from the personnel corridor or the ISO-5 (Class 100) aseptic fill room #FF2-016.

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	Debra M. Emerson Thomas J. Arista	Debra M. Emerson, Investigator Thomas J. Arista, Investigator	11/13/09

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 781-596-7700	10/8/09-11/13/09
	FEI NUMBER 1000305672

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Henri A. Termeer, Chairman, President, and CEO

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

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36. There has been no airflow pattern evaluation performed for the (b) (4) Isolators, which are used for Sterility Tests of various finished products. The evaluation of airflow assists to determine airflow dynamic and turbulence created by the tests equipment and load configurations within the Isolator, which in turn assists to determine the appropriate placement (e.g., worst case) of the Chemical Indicators (CIs) challenges. In addition,

- There is no data to support the placement of the CIs. The CIs determine the presence or absence of the vaporized (b) (4) on the work surfaces and worst case locations within the Isolator to decontaminate.

- The place of the CIs also assists to determine the worst case challenge locations for the (b) (4) Biological Indicators (BIs). However, in the absence of the airflow pattern evaluation to support the placement of the CIs, there is no data to support the validity of the worst case challenge locations for the BIs.

- There is no record to document the rationale for the worst case load configurations for the Sterility Tests Isolators.

- There is no record to document the CIs that were used in support of the October 2008 Isolator requalification. In addition,

- There is no rationale for the placement of the thermocouples within the Isolators.

- There is no established written procedure that describes the manner with which the BIs and CIs are attached to the thermocouples during the requalification.

37. The most recent vendor audits of the BI and CI manufacturers did not include assistance from the microbiology departments, which would provide a scientific evaluation of the vendor's microbiology methods of analysis in support of the BIs and CIs.

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38. The Isolator gloves are checked for leaks and holes via a so-called (b) (4) '. However, there is no written procedure to describe the (b) (4)

39. Cerezyme manufacturing process has not been updated to reflect cGMP's.

- Current industry standard when manufacturing with animal derived cells calls for (b) (4) steps. The Cerezyme process has (b) (4)

40. Process validation is incomplete:

- Microfiltration skid membrane for Cerezyme manufacturing is not validated for its reuse.
- Insufficient biochemical testing to support eluate hold times during the Cerezyme purification process.

41. Quality Assurance oversight of control processes is insufficient:

- Cerezyme release specifications for drug substance and drug product do not reflect manufacturing history and process capability.
- There is no release or in-process testing on th (b) (4) n state of (b) (4) e residues (a critical quality attribute).
- As a corrective action to a previous FDA 483 issued in 2008, a technical report was written and was approved by quality on 4/24/09. This report provided additional specifications for (b) (4) (b) (4). There is no procedure or process in place to evaluate or implement information derived from these technical reports. In August 2009, the batch records for the (b) (4) buffers were changed to include these additional specifications listed in the technical report. On 5/8/09 (b) (4) was manufactured. This buffer is used in purification of Cerezyme at the (b) (4). The conductivity listed in the batch record was recorded as (b) (4) n. The approved technical report listed the specification range for the conductivity of this particular buffer (b) (4) Prior to this inspection, there was no evaluation by quality into the conductivity result which was documented in this batch record.

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42. For raw material:
- There is no tracking or trending of failed incoming raw materials.
- There is no notification outside of QC that a lot of raw material has failed upon receipt. In addition, this information is not always provided to the Genzyme inspection team for audits unless a SCAR is written.
- The firm does not normally change the incoming requirements for inspection of raw material even if the material failed during the last inspection.
- The personnel gowning worn in the filling suite is sterile. The firm has never tested their jumpsuits, hoods, booties, or goggles to confirm sterility.

43. For incoming of (b) (4) they us (b) (4) for identity. The firm's procedure entitled: Sampling Procedure for Raw Materials, QC-048-72, requires that identity samples be from each container of a given lot. On 2/8/08, (b) (4) (b) (4) were received. This lot of (b) (4) was then assigned Genzyme part number (b) (4) and Genzyme lot number 923945.
- One of the identity tests is (b) (4) Viscosity. In reviewing the data for lot 923945 it was noted that the firm conducted the (b) (4) Viscosity test off of a composite sample. It was explained that individual bottles should have been tested.
- Another identity test is (b) (4) The data reviewed for this lot included one sheet that documented only one analysis was run. It was explained that individual bottles should have been tested.

44. Some procedures reviewed are not reflective of the firm's current practice. For example:
- The procedure entitled: Operation of the (b) (4) (b) (4) effective 10/13/09, allows operators the option to (b) (4) of drug product. The last lot of product, Cerezyme A8062, run using indirect filtration was on 11/3/08.
- The procedure entitled: Preventative Maintenance Process Procedures Using the (b) (4) Computerized maintenance Management System at Allston Landing, PM-023-70 was changed effective 2/11/09 to remove the requirement that quality needs to review preventative maintenance documents. The procedure for "Maintenance of the (b) (4) Lyophilizer and (b) (4) ' effective 10/6/09 (b) (4) requires quality to perform final review of all maintenance logs. Quality review of the lyophilizer maintenance documents was discontinued as of January 2009 but the individual equipment procedure has not yet been updated.
- A cleaning-in-place procedure used a (b) (4) check to ensure that water was flooding the pipes. The (b) (4) check was not incorporated into the SOP.
- After a (b) (4) assay was performed in the QC lab, the data was compared against historical data in the Allston Landing (b) (4) . This practice of trending results was not incorporated into the SOP.

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45. The "Preliminary Manufacturing Investigation Procedure in response to Out-of-Specification (OOS) or Unexpected results at Allston Landing" document @100-32, dated 9/30/09 establishes that a "preliminary manufacturing investigation will be initiated upon receipt of notification of OOS or atypical non-failing value via the respective attachment in QC-019-05." However, the Fabrazyme intermediate lot number (b) (4) (b) (4) collected on 4/22/2009 (b) (4) collected on 5/16/2008 (b) (4) were not on the list. DM 11/13/09

46. According to the "Qualification of PTS Cartridges / Analysts and Validation of Samples using the (b) (4) Test System", validation document #QC-051-40, effective 04/25/08, establishes the (b) (4) acceptance criteria for running this assay is between (b) (4) The December 4th and 8th, 2008 (b) (4) samples fell outside of the (b) (4) and (b) (4) respectively. Despite (b) (4) acceptance criteria established in the validation document, the tests were still approved.

47. The firm uses wet lines for their sprinkler system. The firm has covers over all in house sprinklers. The system is deficient in that:
    - The firm has not inspected each individual sprinkler in house since the system was originally installed.
    - The as built drawings for the location of the individual sprinklers were reviewed. The as-built drawings do not reflect the placement and location of all sprinklers at current day.
    - The firm had a stainless steel housing mounted around the sprinklers in the class 100 fill suite. The firm does not have a drawing or diagram for these sprinkler housings.

48. Training of employees is insufficient in that:
    - Personnel are performing routine job functions without being trained on the current approved procedures. For example, a quality fill finish inspector performed AQL visual inspections on three lots of drug product (Fabrazyme A9007, Thyrogen A9003, and Fabrazyme A9006) without being trained on current version of the following procedure: Inspection of the Finished Vial Product (unlabeled) Using the (b) (4) Machine at Allston Landing, QA-006-05.

49. The quality group has not approved all as-built drawings and floor plans on site.
    - An error was identified on the current floor plan, the filtration room F-9 was drawn with no door to enter the room, QA had not reviewed this floor plan.
    - On 10/15/09, the diagram was corrected but the engineer did not correct the square footage in the room. This document was not reviewed by QA.
    - Prior to May 2009, when floor plans were changed, the older floor plan was discarded and it was replaced with the modified floor plan without any review or approval by quality.

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Timothy Hawrylok
Dennis Guilfoyle
Richard Ledwidge
22 of 45

The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or

2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgement, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."