DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
22215 26th Avenue SE, Suite 210 Bothell, WA 98021 (425) 302-0340 Industry Information: www.fda.gov/oc/industry	2/18/15 to 3/18/15
	FEI NUMBER 3007934434

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: David A. Carlson, Senior Director Manufacturing

FIRM NAME	STREET ADDRESS
Genzyme a Sanofi Company	2625 162nd Street SW
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Lynnwood, WA 98087	Bulk drug substance manufacturer

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

The following Observations pertain to the production and testing of sargramostim bulk drug substance (BDS) intended to be a component of Leukine (sargramostim/rhu GM-CSF, STN 103362) a sterile injectable drug product.

QUALITY SYSTEM

OBSERVATION 1

Genzyme Northpointe (the firm) Quality unit failed to establish adequate controls to prevent the introduction of microorganisms during the production of sargramostim BDS as evidenced by non-host contamination events. The following laminar flow hoods (LFH) and biosafety cabinets (BSC) are "unclassified" air quality environments used for firm-identified "aseptic operations" when the BDS production materials and/or production material contact surfaces are exposed to the surrounding environment (open step). Because the LFHs and BSC are unclassified, the existing viable microbial surveillance program is insufficient to verify the adequacy of physical and procedural controls to prevent the introduction of microorganisms during open step "aseptic operations", insufficient to conduct investigations for non-host contamination events, and insufficient to determine appropriate corrective action to prevent repeated non-host contamination events.

A) LFH 17325, LFH 17323, and BSC 17324 have open step "aseptic operations" before host-cell (cells containing the expression vector for rhu GM-CSF) expansion in media under conditions that would also expand non-host contamination. The firm experienced the following non-host contamination events associated with GMP production that were detected in or after host-cell expansion: Deviation 210275 was opened to investigate non-host growth Bacillus cereus/thuringiensis/mycoides, and Bacillus megaterium in two of (b) (4) aliquot vial samples of a new working cell bank (WCB); Deviation 165838 was opened to investigate non-host contamination Bacillus cereus/thuringiensis/mycoides detected in (b) (4) fermentation vessel; Deviation DOR 11003 was opened to investigate non-host contamination Enterobacter cloacae detected in (b) (4) fermentation vessel; and Deviation

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	CSO Jen-Jen Sui Chemist James Stuart Chemist Lynda Perry, microbiologist	Barbara J. Breithaupt, CSO; James S. Stuart, Chemist; Jen-Jen Sui, Chemist; and Lynda L. Perry, Microbiologist	03/18/2015

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DOR 10797 was opened to investigate non-host contamination Bacillus cereus/thuringiensis/mycoides detected in (b) (4) Fermentation vessel.

1) LFH 17325 is an unclassified area in Room (b) (4) ("Grade (b) (4) with acceptance criteria matching USP (b) (4). LFH 17325 is used for shake flask inoculation, WCB production, and to aliquot WCB vials after a period of cell expansion. Firm personnel confirmed flask inoculation and WCB production have open step "aseptic operations" before cell expansion in media. Following cell expansion, the open system WCB vial aliquot steps are performed by multiple operators in rotation for a duration estimated to be about (b) (4) (b) (4). The existing microbial controls and surveillance in LFH 17325 are insufficient to prevent and rule-out possible sources of contamination. The following is not intended to be a comprehensive list:

- LFH 17325 is an unclassified area in Room (b) (4) classified "Grade (b) (4)".
- There are no settle plates during the "aseptic operations" in LFH 17325.
- There is no personnel monitoring (fingertip or gown contact plates) after the "aseptic operations" to rule out personnel as a source of non-host contamination.
- There is no in-process viable air monitoring during the "aseptic operations" in LFH 17325.
- Process specific monitoring under SOP T-3000-08 section 8.3, performed only after operations, consists of one viable air sample in the LFH and two viable surface samples.
- There is no operator performance qualification for the WCB "aseptic operation steps".

2) LFH 17323 is an unclassified area in Room (b) (4) ("Grade (b) (4) with acceptance criteria matching USP (b) (4). LFH 17323 is used for media filtration and in-process feed preparations such as the (b) (4) (b) (4) and for the production of WCB in a shake flask. Deviation DOR 10797 opened to investigate non-host contamination Bacillus cereus/thuringiensis/mycoides reported the operator briefly touched the dip tube to the back of the LAF while preparing the (b) (4). Firm personnel identified LFH 17323 as the only area used to prepare the (b) (4), and confirmed the (b) (4) preparation operations include open system steps after (b) (4) filtration and before (b) (4) cell expansion. The existing microbial controls and surveillance in LFH 17323 are insufficient to prevent and rule-out possible sources of contamination. The following is not intended to be a comprehensive list:

- LFH 17323 is an unclassified area in Room (b) (4) classified "Grade (b) (4)".
- There are no settle plates during the "aseptic operations" in LFH 17323.

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• There is no in-process viable air monitoring during the "aseptic operations" in LFH 17323.
• There is no personnel monitoring (fingertip or gown contact plates) after the "aseptic operations" in LFH 17323 to rule out personnel as a source of non-host contamination.
• There is no periodic viable surface monitoring in LFH 17323 where "aseptic operations" are performed. Viable surface monitoring in room (b) (4) under SOP T-3000-08 Attachment 7 is only performed on the walls once every (b) (4) .
• Viable air quality monitoring in Room (b) (4) is performed under SOP T-3000-08 section 8.1.2. The frequency of (b) (4) is not representative of the production frequency in LFH 17323 described as every (b) (4) (b) (4) when a production campaign is in progress.
• There is no operator performance qualification for the media component preparation "aseptic operation" steps.

3) BSC 17324 is an unclassified area in Room (b) (4) ("Grade (b) (4) with acceptance criteria matching USP (b) (4)) used for preparation of hazardous media components such as (b) (4) (b) (4) BSC 17324 is used for media filtration and in-process feed preparations of media components used in (b) (4) (b) (4) and for the expansion of WCB (host cells) in a shake flask. Production personnel confirmed the open step media component preparation is after (b) (4) filtration and before (b) (4) cell expansion. The existing microbial controls and surveillance in BSC 17324 are insufficient to prevent and rule-out possible sources of contamination. The following is not intended to be a comprehensive list:
• BSC 17324 is an unclassified area in Room (b) (4) classified "Grade (b) (4).
• There are no settle plates during the "aseptic operations" in BSC 17324.
• There is no in-process viable air monitoring during the "aseptic operations" in BSC 17324.
• There is no personnel monitoring (fingertip or gown contact plates) after the "aseptic operation" in BSC 17324 to rule out personnel as a source of non-host contamination.
• There is no periodic viable surface monitoring in BSC 17324. Viable surface monitoring in room (b) (4) under SOP T-3000-08 Attachment 7 is only performed on the walls once every (b) (4)
• Viable air quality monitoring in Room (b) (4) is performed under SOP T-3000-08 section 8.1.2. The frequency of (b) (4) is not representative of the production frequency in BSC 17324 described as every (b) (4) (b) (4) when a production campaign is in progress.
• There is no operator performance qualification for the media component preparation "aseptic operation" steps.

B) LFH 17317 is used for multiple open step "aseptic operations" after (b) (4) filtration to sublot (dispense) BDS into bulk bottles and sample from the BDS bulk bottles using (b) (4) The BDS dispensing and sampling operations are performed at ambient room temperature for a duration estimated at (b) (4). The BDS dispensing and sampling operations intermittently expose BDS and BDS contact surfaces when bottles are uncapped and re-capped, and (b) (4) are removed from protective wrappers in LFH 17317. The dispensed and sampled BDS is not immediately frozen; and the (b) (4) storage conditions could allow microbial growth. Under SOP X-0024-40 "Receipt, Storage, Freezing, Thawing, Shipping and Disposal of Bulk Drug Substance (BDS)", effective 16 Jan 15, section 8.2.1, BDS may be stored at (b) (4) for a period not to exceed (b) (4). Review of BDS storage information found actual storage times ranged from (b) (4) at (b) (4).

LFH 17317 is an unclassified area in Room (b) (4) ("Grade (b) (4) with acceptance criteria matching USP (b) (4) (b) (4)). LFH 17317 is used for BDS filtration and dispensing into bulk bottles, BDS sampling out of the bulk bottles after dispensing, re-sublotting bulk bottles (parent) into additional (child) bulk bottles, and BDS sampling out of the re-sublotted parent and child bulk bottles. Firm personnel confirmed BDS dispensing and sampling operations are open system operations performed without further filtration of the BDS. The existing microbial controls and surveillance in LFH 17317 are insufficient to prevent and rule-out possible sources of contamination. The following is not intended to be a comprehensive list:

- LFH 17317 is an unclassified area in Room (b) (4) classified "Grade (b) (4).
- There are no settle plates during the "aseptic operations" in LFH 17317.
- There is no personnel monitoring (fingertip or gown contact plates) after the "aseptic operation" to rule out personnel as a source of non-host contamination.
- There is no in-process viable air monitoring during the "aseptic operations" in LFH 17317.
- Process specific monitoring under SOP T-3000-08 section 8.3, performed only after operations, consists of one viable air sample in the LFH and two viable surface samples.

C) The firm failed to establish adequate operator qualification for at least the "aseptic operations" in the LFHs and BSC used for flask inoculation, WCB preparation, and media preparation as evidenced by non-host contamination events in upstream production (Deviation 165838, Deviation DOR 11003, and Deviation DOR 10797) and for WCB production (Deviation 210275). SOP P-3013-10 "Operator Qualification of BDS Filtration Procedures at Northpointe Facility", effective 12 Aug 14, is limited in scope to only the BDS filtration, BDS dispensing, and BDS sampling operations. There is no requirement for ongoing operator qualification for personnel performing

"aseptic operations" in the LFH and BSC used for flask inoculation, WCB preparation, and media preparation. There is no operator qualification process to demonstrate "aseptic" technique for WCB production which was described as an estimated (b) (4) hour operation to aliquot cells into vials, with the filling performed by multiple Production personnel with a rotation of "aseptic operations" in the LFH.

D) The firm failed to establish a contingency cleaning procedure, consistent with the manufacturer's instructions, to ensure LFH and BSC are brought back into a service condition suitable for use as an area where "aseptic operations" are performed in the event the blowers are turned off. SOP G-3009-9 "Operation and Gowning Procedures for LFH, BSC, and Fume Hoods In Production Areas at the Northpointe Facility", effective 19 Sep 14, section 8.2.1 reads in part "*** If the blower is not on, turn it on and wait for ≥ (b) (4) for the unit to purge and the airflow to stabilize ***". The (b) (4) Operation and Maintenance Manual for Models (b) (4) reads in part "*** (b) (4) (b) (4) ***".

OBSERVATION 2
The Quality Unit failed to conduct appropriate risk assessments to ensure the safety, identity, strength, quality, or purity of the BDS was not altered.

A) The Quality Unit failed to conduct appropriate risk assessments to determine the need for physical and procedural controls to provide adequate microbial surveillance to detect personnel and equipment performance issues, and to reduce the introduction of microorganisms during the production of BDS. Since 11/17/10 there have been at least four non-host contamination events associated with GMP production that occurred in or following host cell expansion steps: Deviation 210275, Deviation 165838, Deviation DOR 11003, and Deviation DOR 10797. The site SOP J-3001-01 "Risk Management Program", effective 12/19/12, lacked a detailed description of how risk assessments should be performed.

• The Quality unit failed to conduct an updated risk assessment relevant to the media filtration and in-process feed preparation in LFH 17323 and BSC 167324. The most recent "Risk Assessment Northpointe Fermentation Media and Buffers", dated 3/29/08, did not fully describe all the open step "aseptic operations" performed in LFH 17323 and BSC 167324, or the risk for the introduction of microorganisms which could be caused by personnel. The risk assessment lacked adequate justification for the existing microbial monitoring program. As an example, there was

no justification describing why viable surface monitoring in room (b) (4) under SOP T-3000-08 Attachment 7 is only performed on the walls where no aseptic operations are performed, while there is no viable surface monitoring in LFH 17323 located in Room (b) (4) which is where "aseptic operations" are actually performed.

• The Quality unit failed to conduct an adequate risk assessment relevant to the open step "aseptic operations" in LFH 17325 which is used for shake flask inoculation, WCB production, and to aliquot WCB vials after a period of cell expansion; and LFH 17317 which is used to dispense BDS into bulk bottles, sampling from BDS bulk bottles, re-sublotting bulk bottles (parent) into additional (child) bulk bottles, and BDS sampling out of the re-sublotted bulk bottles. "Risk Assessment of Microbial Control in the rhu GM-CSF Manufacturing Process at the Northpointe Facility", dated 7/27/07, was based on calculated risks from microbial contamination and did not fully describe the open step "aseptic operations" performed in LFH 17325 and LFH 17317 or the risk for the introduction of microorganisms caused by personnel. "Risk Assessment of Microbial Control in the rhu GM-CSF Manufacturing Process at the Northpointe Facility" Addendum 1, dated 7/26/10, did not fully describe all the open step "aseptic operations" performed in LFH 17325 and LFH 17317, or the risk for the introduction of microorganisms caused by personnel. "Risk Assessment of Microbial Control in the rhu GM-CSF Manufacturing Process at the Northpointe Facility" Addendum 2, dated 10/25/11, failed to review the 7 Feb 11 Deviation DOR 10797 opened for non-host contamination. Addendum 2, immediately under a table showing the Flask Inoculation and BDS Filtration operations, reads in part "*** For both of these non-sterile unit operations it was determined that BHC Seattle has appropriate engineering and cGMP procedures in place to mitigate possible contamination from personnel, air, equipment and facility sources. The probability of occurrence, quality risk and business risk were determined to be LOW ***".

B) The Quality unit failed to conduct an adequate risk assessment relevant to changes to the CIP cycle intended to clean the (b) (4) used for microfiltration (MF) of BDS. No risk assessment was provided that demonstrated the Quality unit evaluated the risk for potential impact to the (b) (4) from repeated CIP cycles using the increased CIP temperature (b) (4) and the change in the cleaning agent from (b) (4) (b) (4). The MF module manufacturer (b) (4) recommended cleaning temperature for (b) (4) modules, using (b) (4) cleaning agent, was listed as (b) (4). The firm intends to repeatedly clean the MF modules as evidenced with Validation study 3174 "Microfiltration System Membrane Lifetime Performance Qualification", closed in a memo dated 25 Feb 15, which reads in part "*** showed acceptable results for up to (b)(4) uses ***".

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OBSERVATION 3

Quality unit investigations for non-host contamination associated with GMP production did not evaluate potential sources of contamination in order to determine root causes and implement corrective action sufficient to prevent additional non-host contamination events as evidenced by four non-host contamination events (Deviation 210275, Deviation 165838, Deviation DOR 11003, and Deviation DOR 10797). There was no microbial monitoring during the "aseptic operations" that could be used to rule out the unclassified LFH and or BSC as potential sources of contamination. There was no personnel monitoring (such as fingertip plates or gown surface contact plates) to rule out personnel as a possible source for the contamination. Further, in Deviation DOR 10797, a potential source of contamination was ruled out without a scientific basis. The DOR 10797 investigation reported the operator briefly touched the dip tube to the back of the LAF while preparing the (b) (4), however the dip tube contact was ruled out as a potential source of contamination on the basis of the duration of the touch.

OBSERVATION 4

The Quality unit failed to review and approve testing plans used to support the frequency of replenishing the CIP cleaning agent prior to executing the tests. CAPA 227747, created 10/30/14 under Deviation 222252, was used to establish the frequency of (b) (4) cleaning agent replacement on the CIP system used to clean (b) (4) (b) (4). The firm reported the use of a (b) (4) Chlorine Test (b) (4), kit (b) (4) (Model (b) (4) to determine the "active chlorine in bleach washes". There was no test plan used to describe the test method, test reagents, appropriate test controls, test samples, pre-determined acceptance criteria, test documentation, or to approve the execution of the test plan by Production personnel. The only documentation of the test results provided during the inspection was a typed sheet of the final values after calculation with the header "Free Chlorine Results for Deviation #222252". It was not possible to verify who conducted the testing or the analytical testing qualifications of the personnel. The firm said multiple Production people were involved in collecting the analytical data. There were no original source data or calculations to show the final test values for free chlorine were accurate. There were no controls in the (b) (4) test kit to verify the kit function, and there was no determination the kit was suitable for the intended use. There was no justification to describe how the (b) (4) replenishment of (b) (4) was supported by test results purported to have been collected for only a fraction (9/23/14 to 10/15/14) of the intended (b) (4) month duration for replenishment.

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OBSERVATION 5

The Quality unit failed to follow SOP Q-0059-15 "Guidelines for Analytical Test Method Validation", effective 12/18/13, section 10.1 which reads in part "*** analytical procedures used for testing must be validated, qualified, and/or verified for intended use according regulatory and compendial requirements ***" by accepting the (b) (4) test results used as part of CAPA 227747 "Modify frequency of (b) (4) replacement on the CIP system". created 10/30/14. On 11/26/14, the Quality unit representative approved the CAPA to implement the Plan Details which reads in part "*** Engineering will completely empty and refill Bleach tank UC-6301-01 on a (b) (4) basis ***".

LABORATORY SYSTEM

OBSERVATION 6

Not all test methods have been adequately verified.

A) The microbial content assay for BDS and in-process material (SOP T-3011-07, "Microbial Content Assay,") uses only (b) (4) plates incubated at (b) (4) °C to enumerate microbial content of these materials. The validation study QCTD-T3011-020111, "Norhtpoint In-Process and Sargramostim BDS Materials Confirmation Study," validates the method using the same medium and incubation temperature. The validation provides no assurance that this incubation scheme is equivalent to the method required by USP <61>,"Microbiological examination of nonsterile products: microbial enumeration tests," for the method's intended use.

B) The validation study QCTD-T3011-020111, "Norhtpoint In-Process and Sargramostim BDS Materials Confirmation Study permits retests in the event of failure to meet acceptance criteria, but there were no written controls governing the number of retests that could be allowed. There were 2 failures out of (b) (4) tests (retests included) in the validation for BDS testing and a total of six failures over all (b) (4) materials for which an assay was validated. Of these, five were speculated in the validation report to have possibly resulted from difficulties with the preparation of suitable homogeneous cultures to serve as inocula. There is no assurance that these failures are unrelated to the reproducible performance of the microbial content assay itself.

C) The SOP T-3011-07, "Microbial Content Assay," specifies a hold time of (b) (4) or less at (b) (4) °C for BDS

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microbial content samples, and (b) (4) or less at (b) (4)°C for (b) (4) in-process microbial content samples that are not tested immediately. These hold times are validated for the current manufacturing process by study QCTD-T3011-020111. This validation includes only three reference microorganisms with no assurance that they are representative of the microorganisms that are at greatest risk of being found in these materials.

D) SOP T-3000-08, "Viable Air and Surface Monitoring Procedure (Northpointe Facility)," requires that surface monitoring be performed with (b) (4) contact plates that are incubated at (b) (4) °C. Validation of recovery of microorganisms from surfaces by the contact plates using a single incubation temperature of (b) (4) °C is described in validation protocol and report QCMV-T3000-091508P, "Validation of Northpointe Viable Surface Testing and Incubation Procedures," and QCMV-T3000-091508R, "Validation of Northpointe Viable Surface Testing and Incubation Final Report." The validation compares recovery of a panel of microorganisms from surfaces by (b) (4) with recovery by (b) (4) (b) (4). The acceptance criteria were changed after approval of the protocol to omit consideration of one of the challenge microorganisms, (b) (4) which was found to be recovered poorly by (b) (4) (b) (4) compared to its recovery by (b) (4). The validation report explains the unimportance of the failure of (b) (4) to recover (b) (4) (b) (4) by stating that (b) (4) is unlikely to be present on surfaces. No risk assessment was documented to support the appropriateness of the selected challenge microorganisms as representative of the microorganisms found in the manufacturing environment.

E) There is no formal program of ongoing validation to support the continuing use of (b) (4) plates incubated at (b) (4) (b) (4)°C as the sole incubation scheme used for air and surface monitoring as per SOP T-3000-08, "Viable Air and Surface Monitoring Procedure (Northpointe Facility)." Validation of the above media /incubation scheme was documented for surface testing by protocol QCMV-T3000-091508P, "Validation of Northpointe Viable Surface Testing and Incubation Procedures" and in Report QCMV-T3000-091508R, "Validation of Northpointe Surface Testing and Incubation Final Report." QCMV-T3000-091508R was approved on August 18, 2009. Validation of the above media /incubation scheme was documented for viable air testing in protocol QCMV-T3000-012507, "Validation of Northpointe Viable Air Testing and Incubation Procedures" and in Technical Report QCMV-T3000-012507, "Validation of Northpointe Viable Air Testing and Incubation Procedures." QCMV-T3000-012507 was approved on December 18, 2007. Without ongoing validation there is no assurance that these methods remain capable of detecting all aerobic heterotrophic microorganisms, including yeasts and molds,

currently found in the manufacturing environment.

OBSERVATION 7

There is no written policy governing critical aspects of method development and validation studies that are unique to microbiological assays. SOP Q-0059-15, "Guidelines for Analytical Test Method Validation," and SOP Q-0274-04, "Quality Control Method Development, Qualification and Technical Studies" do not address policy or guidelines regarding microbiology-specific issues including CFU ranges that should be considered countable, selection of challenge organisms, or how and when to use actual environmental monitoring data in a validation study.

OBSERVATION 8

Appropriate written procedures designed to prevent contamination of BDS substance and in-process materials by objectionable microorganisms have not been established.

The disinfectant efficacy validation protocol and study, QCMV-G3002-042210, "Validation of Cleaning Agents for the Northpointe Facility April 2010" and QCMV-G3002-042210R, "Validation of Cleaning Agents and Neutralizing Media for the Northpointe Facility," allows a valid enumeration of untreated control organisms to be based on an average as low as (b) (4) Cfu per plate. Microbial enumeration methods based on plate counts typically establish minimum acceptable CFU criteria based on a sound statistics-based rationale. Acceptance of low numbers of CFUs unneccessarily reduces accuracy and thereby reduces the level of assurance that the log reduction acceptance criteria for the disinfectant treatments have actually been met. A control enumeration based on an average of (b) (4) CFU per plate was used in this validation study at least once, on June 15, 2010. (b) (4) was the challenge organism and the coupon material was (b) (4) (b) (4).

OBSERVATION 9

All laboratory records do not include the signature of a second person showing that the original records have been reviewed for accuracy.

Microbiological tests in which the results are read by an evaluation or enumeration of microbial growth on agar plates are not completely reviewed for accuracy because the reviewer is not required to observe the microbial growth. The written control governing review of documents is SOP Q-0185-23, "Performing Assays and Reviewing Test Results." Individual test method SOPs including T-3011-07, "Microbial Content Assay," SOP T-3000-08, "Viable Air and Surface Monitoring Procedure (Northpointe Facility)," SOP T-3008-12, "(b) (4) (b) (4) Collection and Microbial Content Testing Procedures,"SOP T-3006-06, "Non-Host Assay at the Northpointe Facility" and SOP T-3005-11, "(b) (4) and Identification Procedures" also fail to instruct reviewers to confirm evaluation of plates.

OBSERVATION 10

Laboratory records do not include a statement of how the results compare with established standards of quality.

Growth promotion testing of microbiological media performed according to SOP #T-0106-28, "QC Microbiology Media Qualification Procedure," does not adhere to the requirements of USP <61>, "Microbiological examination of nonsterile products: microbial enumeration tests," which require plating of a standardized inoculum of microorganisms to result in plate counts not differing by a factor more than two from plate counts obtained by plating on control media. As a result, (b) (4) plate media,(b) (4) lot 3071057, received April 4, 2013, was qualified on April 29, 2013 based in part on growth of (b) (4) CFU of (b) (4) on test media compared to (b) (4) CFU on a previously qualified lot. This improperly qualified lot (b) (4) was used to perform the non-host assay on in-process sample material (b) (4), testing initiated between August 9, 2013 and August 16, 2013. (b) (4) plate media, (b) (4) lot number (b) (4), received July 30 2013, was qualified on August 16, 2013 based in part on growth of (b) (4) CFU of (b) (4) (b) (4) compared with (b) (4) CFU on a previously qualified lot. This improperly qualified media was used to perform the non-host assay on in-process material number (b) (4), testing initiated on August 21, 2013.

OBSERVATION 11

Training of laboratory personnel does not ensure that personnel possess the experience required to perform their

assigned functions.

OJTD # WSH-OJT-QCB-007-00, "Media qualification," establishes on-the-job training requirements that must be accomplished before a trainee can be permitted to perform media qualification. Requirements include supervised performance of (b) (4) media qualifications, but the trainee is not required to demonstrate proficiency through achievement of satisfactory results. On March 28, 2014, a trainee performed a media qualification for training purposes on a previously qualified lot of (b) (4) Records indicate that 0 CFUs were found on the test plate inoculated with (b) (4) and (b) (4) on the control. The test was determined to be invalid as per SOP #T-0106-28, "QC Microbiology Media Qualification Procedure," which requires at least (b) (4) CFU on each plate. The qualification was still counted as one of the trainee's (b) (4) required qualifications. A representative of the firm explained that the trainee's performance was acceptable because the trainer watched the trainee perform the test and observed that the trainee correctly followed all of the requirements of the relevant SOP.

OBSERVATION 12

There are no equipment identifiers for desiccators, no systematic maintenance of the desiccators, and there is no documentation of desiccant changes or performance checks. (b) (4) desiccators in room (b) (4) were identified " (b) (4) " respectively and contained raw material retention samples sorted by (b) (4) (b) (4) expiry. In the Raw Material Quality Control laboratory, room (b) (4) (b) (4) additional uncontrolled cabinet style desiccators were discovered under a bench cabinet identified "QCRM RAW MATERIAL SAMPLE STORAGE". Analysts were reported to have changed the desiccant when they noticed it needed to be changed. The firm has failed to identify these desiccators as GMP non-Critical Instruments per SOP # V-3002-03 "Qualification of GMP Bench Top Equipment and Analytical Instruments".

OBSERVATION 13

The firm failed to validate the Total Organic Carbon (TOC) analysis at the Genzyme Northpointe location. The Firm's Quality Control Method Validation Summary QCMV-0131 "Revision of Water Chemistry Testing (SOP #T-0166)" and "Implementation of System Suitability for TOC (SOP #T-0166)" concludes that the expiration date for system suitability solutions will be set at (b) (4) when stored in (b) (4) ° C. This Revision of Water Chemistry Testing was conducted at the end of 1997, in a different facility and using different equipment. The firm failed to

replace QCMV-0131 when changes to the process occurred such as changes in equipment, sample handling, and changes to location when the firm moved operations from Seattle to Lynnwood, WA. The failure to validate the TOC analysis is not consistent with SOP # V-0006 "Change Control", section 8.4 "Change Control Impact Assessment Gathering"; it should have been noted that QCMV-0131 was relevant to a previous testing location. Additionally the implementation of SOP # D-3008 "Change Control Program" in June of 2014 should have evaluated all extant analytical method validations for the effects of change. TOC analysis is used to assess water quality at several points in the GMP process. Further, QCMV-0131 was flawed in that the test samples were not compared to freshly made standards; the standards used had been stored in (b) (4).

OBSERVATION 14

Four of five Laboratory personnel training records were overdue for parts of their curriculum which are required by section 8.2 of SOP# I-0002-33 "Current Good Manufacturing Practices (cGMP) Training program", and section 9.14 of SOP #I-3000-05 "Qualification Program".

- (b)(6),(b)(7)(C) has one item 92 days overdue, (b) (4) Test Method Assessment Exam.
- (b)(6),(b)(7)(C) has one item overdue by 2 days. WSH-SOP-T-0085; (b) (4) (b) (4)
- (b)(6),(b)(7)(C) has one item overdue by 1 day, WSH-SOP-T-0209: (b) (4) (b) (4).
- (b)(6),(b)(7)(C) has one item overdue by 1 day, WSH-SOP-T-0164: USP Antimicrobial Effectiveness Testing (b) (4)

PRODUCTION SYSTEM

OBSERVATION 15

There was no validation data to show the increase in CIP temperature (b) (4), and the change in the cleaning agent (b) (4) will not adversely impact the (b) (4). Validation Document #4531 "Validation of the Cleaning Procedure for the Microfiltration System Protocol", Final Report

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
22215 26th Avenue SE, Suite 210 Bothell, WA 98021 (425) 302-0340 Industry Information: www.fda.gov/oc/industry	2/18/15 to 3/18/15
	FEI NUMBER 3007934434

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: David A. Carlson, Senior Director Manufacturing

FIRM NAME	STREET ADDRESS
Genzyme a Sanofi Company	2625 162nd Street SW
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Lynnwood, WA 98087	Bulk drug substance manufacturer

signed by QA on 2/18/15, failed to provide data to demonstrate the BDS production contact surfaces of the (b) (4) MF modules are not reactive, additive, or absorptive after repeated CIP cycles with a different cleaning agent than previously validated, and a higher temperature than recommended by the manufacturer of the MF modules.

OBSERVATION 16

The procedure to periodically verify appropriate personnel access to automated equipment in at least the Fermentation area is inadequate. There is no documentation demonstrating that access was verified for the area's current personnel and the access level was appropriate to the person's role. SOP G-3027-05, effective 6/20/14, section 8.3.1 reads in part "***Access request forms will be reviewed annually ***". SOP G-3027-05 section 8.3.1 lacks a description of how to verify access, how the review will be performed or who will be involved with the access review.

	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
SEE REVERSE OF THIS PAGE	CSO, Jen-Jen Sui, chemist, James Stuart chemist, Lynda Perry, microbiologist	Barbara J. Breithaupt, CSO; James S. Stuart, Chemist; Jen-Jen Sui, Chemist; and Lynda L. Perry, Microbiologist	03/18/2015