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I. Summary

The pre-approval inspection of this drug substance manufacturer, Genzyme Corporation, 8 New York Avenue, Framingham, MA FEI: 1220423 was initiated according to eNSpect Assignment #170211, for profile code CBI. The inspection was conducted in support (b) (4) (b) (4), applicant (b) (4). The inspection was risk-based and conducted in accordance with applicable sections of CP 7356.002M - Inspection of Licensed Therapeutic Drug Products; CP 7346.832 - Pre-approval Inspections/Investigations and ICH Q7. The inspection was limited to (b) (4) drug substance manufacture.

The prior inspection was a GMP and PAI conducted from 01/23 - 02/02/2018 by NEW-DO. Quality, Production, Facilities and Equipment, and Laboratory Control Systems were covered. No Form FDA 483 was issued, with the inspection classified NAI.

This pre-approval inspection covered Quality, Facilities and Equipment, Production, Materials and Laboratory Control Systems. No refusals were encountered, and no samples were collected during the inspection. At the conclusion of the inspection on 04 September 2020, a 2-Item Form FDA 483 **(see Attachment 1)** was issued to Ms. Lisa McClintock, Site Head Framingham Biologics regarding the following objectionable conditions:

1) Facilities and equipment supporting manufacture are not adequately maintained.
2) Equipment used within the QC Microbiology Laboratory has not been adequately certified and review of logbooks has not been conducted according to procedure.

In addition, 6 verbal discussion items were discussed with the firm.

II. Administrative Data

Inspected firm:	Genzyme Corporation,
Located at:	8 New York Avenue
	Framingham, MA 01701
Phone:	508-271-6938
FAX:	N/A
Mailing Address:	Same as prior address

The inspection team consisted of the following members:

Wayne Seifert, CDER/DBM1 (WS)
Ying-Xin Fan CDER/OBP (YXF)

Dates of inspection: August 26 - September 4, 2020
Days in the facility: 8 days

We (WS and YXF) presented to Ms. Lisa McClintock our credentials at the beginning of the inspection on 26 August 2020, along with the Form FDA 482 (**Attachment 2**). Immediately after the firm presented an overview of the facility and organization structure, see **Exhibit WS-1**, we proceed on a tour of the facility.

The lists of attendees present at the opening meeting and at the closeout meeting are provided under **Exhibit WS-2.** During the inspection closeout meeting on 4 September 2020, an FDA Form 483 was issued to Ms. Lisa McClintock, see **Attachment 1**.

III. History

The 8 NYA Integrated Continuous Biomanufacturing Facility is (b) (4) ft^2, with core office business hours 9 AM - 5 PM, with operations (b) (4). There are (b) (4) Manufacturing employees,

(b) (4) Quality, (b) (4) employees in other functions and (b) (4) Framingham Biologics employees in total. For the facility history overview, see **Exhibit WS-1.**

IV. Interstate Commerce

This inspection was limited to (b) (4) drug substance manufacture, with the product currently approved for manufacture at 74 NYA, will the PAI for 8 NYA (b) (4) manufacture.

V. Jurisdiction (Products Manufactured and/or Distributed)

Products manufactured and distributed at the Genzyme Corporation, Framingham campus are summarized as follows:

(b) (4)

VI. Individual Responsibilities and Persons Interviewed

The Genzyme Corporation, Framingham, MA organizational chart is provided under **Exhibit WS-1**, with a list of all individuals interviewed during the inspection included under **Exhibit WS-2**. A daily wrap meeting was held each day of the inspection.

VII. Firm's Training Program

This section written by WS

On 03 September 2020, Mr. Marcos Carreras-Vargas, Associate Director of Learning and Development provided an overview of the training program according to BQ-PLN-000006, "(b) (4) *Training Plan"*, v3. Effective date 10/04/2020. The scope of the procedure is minimum compliance training and GMP refresher. The validated application in support of training is My Learning Center. I reviewed BQ-GOP-00009, *"Training System for the Biologics Network"*, v5, Effective date 03/09/2019. The scope of the procedure is overall training, onboarding (new hire, Genzyme background, good documentation practices, etc.). The training curriculum for an employee is determined by management with QA approval of procedures for training. Training may include On-The-Job (OJT), instructor led, and corporate based. There were no individuals past due for training at 8 NYA from a GMP perspective.

No objectionable observation was identified.

VIII. Manufacturing and Design Operations (Tour)

This section written by WS

On 26 August 2020, we (WS and YXF) proceeded to 8 NYA, the materials receiving dock, with all raw materials sampled, tested and released at the (b) (4) facility. A Genzyme dedicated (b) (4) transports the materials between buildings, with the inspection of the materials upon receipt according to delivery order that includes absence of damage. Materials within the GMP warehouse are stored electronically within Athena, a validated module within SAP. The GMP warehouse includes (b) (4) temperature probes for continuous temperature monitoring and (b) RH probes. I (WS) requested an SAP printout of the materials stored in location JIT/E4A that consisted of 3 drums of (b) (4), with the quantity accurate. Wooden pallets are not accepted into the building, with material transfer at the (b) (4) facility onto (b) (4) pallets.

We proceeded to the weigh and dispense area (view from outside corridor) that contained (b) (4) downflows with 100% HEPA filter coverage. Materials for manufacture are weighed into bags designed for attachment to the single use (b) (4) manufacturing bags within (b) (4) (b) (4). Only one component is weighed at a time, but weighs may continue to complete a formulation without area clean. An area clean is conducted when all materials have been weighed in support of a formulation.

We proceeded to the material (b) (4) 1204 (MAL) where materials for entry into Suite (b) are sanitized with (b) (4), with a cart to cart transfer within the (b) (4). Materials within the suite are further sanitized with (b) (4).

We proceeded to the 2 - 10°C Cold Room 1131 used for drug substance storage. Laboratory standards were currently being stored in the area.

We proceeded to the upstream area, CNC space, where a ceiling diffuser screen was not attached securely to its ceiling mount. The cause was associated with an unsecured fastener. Other diffuser screens were observed with a similar issue, unsecure fasteners, see **Exhibit WS-3**. On 03 September 2020, Mr. Bill Culleton, Sr. Director Facility Operations provided a follow up to the observed diffuser screens, with the fasteners becoming loose over time, with all tightened according to Work Report FRAD20E0729, event record date 27 Aug 2020, see **Exhibit WS-4.**

This resulted in a 483 Observation and is additionally discussed under Objectionable Conditions 1.c, Section X.

We proceeded to the seed lab as observed from the outside corridor that contained a (b) (4) LFCB and incubators. The (b) (4) process is performed by (b) (4) flask in (b) stages, (b) (4). Regarding the (b) (4) flask, a (b) (4) is performed in support of transferring the cells to a (b) (4) bag by tube (b) (4).

We proceeded into upstream where the (b) (4) liter single use bioreactor was located and associated (b) (4) I.D. 2200. Pre-filtered media from the CNC space transitions by (b) (4) tubing into the cell culture area into the bioreactor. Connection of the media to the bioreactor is performed in the CNC space by tube (b) (4), with dispense of the media during the continuous manufacturing process by weight that includes (b) (4) volumes per (b) (4). Bioreactor controls includes (b) (4). The manufacturing process includes the growth phase, harvest for (b) (4), with the overall batch manufacturing process taking (b) (4). (b) (4) sampling includes (b) (4).

The (b) (4) liter bioreactor is connected to (b) (4), followed by (b) (4) micron filters. Both the (b) (4) and (b) (4) micron filters ((b) (4) filters) are not integrity tested, with a breach in an (b) (4) causing the pressure to rise and an alarm condition. The (b) (4) from the (b) (4) is sent to a (b) (4) with a second (b) (4) -liter (b) (4) supporting overflow. Material from the (b) (4) is processed through the (b) (4). Transfer tubing from the (b) (4) is attached to a (b) (4) by tube (b) (4), with approximately (b) (4) of product acquired over (b) (4), followed by the (b) (4). (b) (4) bags of product equates to 1 DS batch. The upstream process is a (b) (4) system supported by (b) (4) (b) (4) components and (b) (4). Upstream contained an area for IPC testing that includes (b) (4). The instruments were standalone, with data networked. Each person accessing the systems has their own user I.D. and password.

We proceeded to Downstream (b) (4) Area (b) (4). The area contained the (b) (4) liter (b) (4) load (b) (4) PBT-2600-001 and associated (b) (4) X-3000001 and (b) (4) X-311020. (b) (4) are attached to the (b) (4) within the CNC area by clean connect attached to a manifold, with (b) (4) connect to (b) (4) with chemical sanitization. The (b) (4) from the (b) (4) is transferred to a (b) (4) liter (b) (4) PBM 3010001, were the drug substance material is stored in (b) (4) at 2 - 8°C pending further processing. (b) (4) make up 1 DS batch, with the (b) (4) in the manufacturing process. I (WS) question the system (b) (4) transfer hoses supporting manufacture, with the hoses on a preventive maintenance schedule and replaced when required. The (b) (4) drug substance within a (b) (4), PBM-3027001 includes the (b) (4), with transfer to a second (b) (4) PBM-3028001. Temperature controlled at (b) (4) C. Transfer to the second (b) (4) and hold time at (b) (4) to (b) (4) is to assure all product is in contact with the (b) (4). There is a spare (b) (4), asset I.D. C-3110010.

The product is transferred to the (b) (4) C-3030001 and (b) (4) C-3110030, with (b) (4) to a (b) (4) PBM-304101, with transfer to (b) (4) liter (b) (4)

PBM-3040001. Both tanks are controlled at (b) (4) °C. The material is transferred to the (b) (4) X305001 and (b) (4) C3110040, with (b) (4) to (b) (4) liter (b) (4) PBM-3060001, (b) (4) °C temperature control, followed by (b) (4) PBM-3060002 (b) (4) liters. The product is processed through the (b) (4) X3070001 that contains a (b) (4) -liter vessel. I (WS) visually inspected through the site glass the condition of the (b) (4) -liter vessel that appeared clean. The process includes (b) (4), with the (b) (4) by clean connect to a (b) (4) liter (b) (4) PBM-3080001, (b) (4) °C temperature control.

(b) (4) filtration occurs, (b) (4) filters, with the (b) (4) physically separated from (b) (4) by a (b) (4), with product piped (b) (4) for filling into bags, storage at 2 - 8°C. A drug substance campaign includes the use of (b) (4) filters.

All (b) (4) are stored in (b) (4) and sanitized with (b) (4).

We proceeded to area 1201, a large area, CNC space for the formulated medias and (b) (4) used in manufacture. The area is at ambient temperature.

We proceeded to the 2 -10°C cold room 1220 used for media and intermediate storage.

We proceeded to media preparation area 1350, Solution Preparation. Raw materials transition through an (b) (4) with cart to cart transfer, sanitization with (b) (4), contact time (b) (4). The area contained separate bays for media manufacture that included (b) (4) consisting of (b) (4). Each (b) (4) has a (b) (4) that is not used in the manufacturing process.

Area1350 contained a room for storage of raw materials, Room 1363. I (WS) questioned if the room was temperature mapped, with the firm indicating that a CAPA was already in-progress to complete the validation activity. We proceeded to room (b) (4), Weigh and Dispense Room, with the area having two separate weigh stations, area DFB-100001 and D101001. Materials weighed under Grade D conditions for manufacture are deducted from SAP. Area DFB-100001 was observed with a return pre-filter dislodged from its mounting, **see Exhibit WS-5.** On 03 September 2020, Mr. Bill Culleton, Sr. Director Facility Operations provided a follow up to the dislodged pre-filter, with Work Report FRAD20E0729, event record date 27 Aug 2020 identifying the reseating of the filter, see **Exhibit WS-4.**

This resulted in a 483 Observation and is additionally discussed under Objectionable Conditions 1.b, Section X.

We proceeded to the water system located in Area 1170, Clean GMP Utilities. Water for further manufacture is acquired from the Framingham reservoir through the municipality, with the water (b) (4) filtered. The pre-treatment system (b) (4) consists of (b) (4)

(b) (4). Water from the pretreatment system feeds directly to the WFI (b) (4), no tank. The (b) (4) qualified WFI (b) (4) are by (b) (4). There is another pretreatment system of equivalent design X9207001 and WFI (b) (4) (b) (4) 9253001 currently under qualification.

The WFI system contains a (b) (4) liter WFI tank, with (b) (4) loops. A second (b) (4) WFI tank is under qualification.

On 27 August 2020, I (WS) proceeded to Building 8 Room 1170, Clean Utilities where the (b) (4) (b) (4) generator by (b) (4) was located, with the system new and absent of leaks. I proceeded to the mezzanine level where two (b) (4) were located, AC-9300001 and AC9300002. Post (b) (4), the (b) (4) is received by (b) (4) The (b) (4) is distributed as process (b) (4) or instrument (b) (4) by two separate lines constructed of (b) (4), with transition to (b) (4) for suite penetration. The process (b) (4) was at a dew point of (b) (4) °C.

On the 28 August 2020, I (WS) proceeded to the outside (b) (4) storage farm consisting of a (b) (4) tank with evaporators, (b) (4) tank, and unconfirmed tonnage (b) (4) tank. The distribution systems are (b) (4) for GMP suite penetrations. The supply transport (b) (4) for the (b) (4) proceeds to 80 NYA where the process (b) (4) is physical checked for I.D., along with the C of A, then to 8 NYA for offload.

On 02 September 2020, I (WS) returned to the WFI production room at 8 NYA. I observed a leak coming from above (b) (4) BV9250010. On 03 September 2020, the firm confirmed the leak as insufficient insulation from the (b) (4) water line, with Work Order 2608649/Work Report FRAD20E0730 provided for corrective action, see **Exhibit WS-6**. In discussion with the firm, the WFI transfer line from the (b) (4) to the storage tank is (b) (4). I observed what appeared to be dried brine under the pretreatment system. On 03 September 2020, the firm indicted the residue under the pre-treatment system as dried brine from an old leak. The dried brine was removed, with corrective action an inspection of the system to take place routinely to assure the absence of leaks, see Work Report FRAD20E0730 provided for corrective action, **Exhibit WS-6**.

On 02 September 2020, we (WS and YXF) proceeded to the Room (b) (4) (access restricted) where the working cell bank (WCB) is stored within a (b) (4) dewar FB-2979, monitored and alarmed by EMS. The dewar was secured by lock and key maintained by Quality. (b) (4) racks hold the labeled (b) (4) and (b) (4) WCB vials, with segregation by separate racks. Upon removal of a cell vial, the vial is scanned into the batch record and placed into a (b) (4) dewar with temperature monitoring for transport to the inoculation seed laboratory.

I (WS) proceeded to Room (b) (4), (b) (4) room containing a (b) (4) FB-2880-001. I observed (b) (4) on the (b) (4) cart, along with a similar condition for the

chamber, see **Exhibit WS-7.** On 03 September 2020, Mr. Kyle Bigness, Sr. Manager -(b) (4)-ICBF Project provided a follow up to the observed (b) (4) cart and chamber condition. I reviewed the work instruction for ancillary equipment, cleaning procedure, electronic work instructions under FBL-EWI-00005, v2, *"Facility and Equipment Disinfection"*, see **Exhibit WS-8**. There is no routine inspection of the (b) (4) and there is no procedure for cleaning of the (b) (4). Corrective action included Work Order 2609026 for investigate and repair stains on the inside of the (b) (4) and cart, see **Exhibit WS-9** and Work Order 2608722, Lock-out (b) (4) and remove residual (b) (4) inside the unit, see **Exhibit WS-10.** Furthermore, a procedure update will occur for routine inspection and cleaning of the (b) (4). Pictures were provided by the firm, with the residual (b) (4) removed from the (b) (4) cart and chamber, see **Exhibit WS-11.**

This resulted in a 483 Observation and is additionally discussed under Objectionable Conditions 1.a, Section X.

Quality Systems

Deviations and Procedure

This section written by WS

On 31 August 2020, Mr. Matthew Offenbacher, Quality Manager provide an overview of the deviation management system, with deviations managed within the validated application Phenix, prior system Trackwise. I reviewed BQ-GOP-000248, *"Plan Deviation Process"*, V4, Effective date 22/07/2020. The deviation process includes management notification and immediate action to prevent harm. A GEMBA, a cross functional team assembles immediately to access cause, with a deviation request within (b) (4) of discovery, and (b) (4) for investigation. Two extensions may be requested, with the first by Quality and the second by the Director of Quality. Deviations are classified as minor, major and critical. A minor deviation review includes the identifier, area responsible and QA expert, with a major deviation review including an investigator lead. A critical deviation requires site head approval. Product must be on the market for assignment of a critical deviation, with the deviation classification determined according to GEMBA, with QA oversight.

I reviewed the CAPA process under Phenix, procedure BQ-GOP-000249, *"Phenix Events and CAPA Process"*, v5, Effective date 10/09/2020. CAPA requirements are determined by QA based on deviation and risk assessment. In the event of a high detection classification for risk, a CAPA is not required. (b) (4) is required in the completion of a CAPA, with exceptions based on complexity (justification) and QA approval.

On 03 September 2020, I reviewed the following deviations associated with out of tolerances:

FRAD20E0096: Opened 11 February 2020, Closed 04 May 2020. The OOT was associated with a trend and specific to FRAD19E0397 and FRAD19E0276 for TOC analyzers where the conductivity did not meet specification during certification. The root cause was instrument

infrequent use, with no impact on testing based on TOC standard within specification at time of instrument use. A (b) (4) flush of the instrument has been instituted as corrective action. No further action was required.

FRAD20E0023: Opened 13 January 2020, Closed 20 April 2020. The OOT was for the filter integrity test units FB-3036 and FB-3032 out of tolerance for flow. The units were adjusted into tolerance. There was no manufacturing impact determined.

FRAD19E0288: Opened 16 August 2019, Closed 22 August 2019. TOC meter on the WFI loop out of tolerance. The tolerance was ± (b) %, with as found (b) (4) %. The analyzer was adjusted into tolerance, with no impact on manufacture.

FRAD20E0464: Opened June 27, 2020, Closed July 24, 2020. The deviation was for Room (b) (4) (Upstream (b) (4)), (b) (4) por (b) (4) with > (b) (4) mg/m^3 recovered for hydrocarbon. The root cause was sample error, with the port retested and acceptable.

FRAD19E0013: Opened May 22, 2019, Closed July 25, 2019. A settling plate under dynamic conditions within the seed LFCB was (b) CFU, acceptance criteria < (b) CFU. The root cause was human contamination. In-process data was reviewed and found acceptable, with the event an isolated incidence. In discussion with the firm, I (WS) questioned if the technician was made aware of the recovery, as for the technician to take an accounting of their aseptic technique. The firm indicated not always.

Reference Discussion Item WS-6 in Section XII, GENERAL DISCUSSION WITH MANAGEMENT.

FRAD19E0251: Opened August 5, 2019, Closed August 6, 2019. Atypical bioburden 8 NYA (b) (4) X3070001 (b) (4) 19MS01141. The post use cleaning was (b) CFU/100 mL, with the acceptance limit < (b) (4) CFU/100 mL. Testing was in specification, but a bioburden event always requires a deviation investigation. A review of the (b) (4) bioburden and endotoxin and downstream testing identified no concerns, with test sample taken by open cup, the most likely root cause of the recoveries. No further action was required.

FRAD19E0297: Opened August 21, 2019, Closed September 5, 2019. Atypical bioburden at the (b) (4) Run 1, (b) (4) Lot (b) (4) C. This was a cycle development run, with sample inadvertently taken pre-mature, prior to required (b) (4) rinse. There was no impact on manufacture.

FRAD19E0247: Opened August 4, 2019, Closed September 6, 2019. The (b) (4) (X3090) (b) (4) pressure high, high alarm. The complete flow path that include the (b) (4) (b) (4) was replaced by tubing (b) (4), with both passing integrity test. The maximum pressure of the (b) (4) were not exceeded, with air entrapment the root cause of the failure. There was no impact on manufacture.

On 04 September 2020, Mr. (b) (6), Quality Engineer Principle, Mr. Derek Pandolfo, Senior Manager Manufacturing, Ms. Kate LaRoche, Manager Quality, and Mr. Armin Opitz, Director, Manufacturing Sciences provided an overview of deviation investigation extensions, where (b) (4) is allowed in the completion of the investigation, with an extension beyond the (b) (4) (b) (4) to be approved by quality. Within the (b) (4) QMS meeting, all records coming due are assessed with QA and representatives determining if an extension is required. The firm does not document the decision process for when an extension is not required. I reviewed the following deviation that was 136 days past due:

FRAD20E0198: Opened 20 March 20, Closure Pending. The deviation investigation is for multiple parameters within the control strategy misaligned in the batch record, not impacting the quality of the drug substance. Corrective actions include a logic function adjustment within the control system that must be tested off line prior to migration to the production environment. The time period beyond (b) (4) is appropriate and justified.

No objectionable observation was identified.

Deviation Related to Leaks

This section written by YXF

TW 356178: Media Transfer Leak from Manifold (Part Number 714049) - Multiple instances (3). On May 06, 2019, during the transfer of Media in room (b) (4) controlled non classified (CNC) area at 8 NYA, a leak was observed from manifold Part Number 714049. The remaining medium was discarded. On May 13, 2019, multiple instances of similar leaks were observed. The filter and all SUT post filter were discarded. There was no product impact as the media in these instances were discarded. The root cause was the manifold not being robust. Change Control 2019FRACC0003 was taken to remediate this design issue with part number 714049. On Sep 01, 2020, Mr. Kyle Bigness, Sr. (b) (4) ICB Project Manager confirmed that this Change Control has been completed and no similar leaks were observed after implementation of the modified manifold.

FRAD19E0094: Leak from (b) (4) L (b) (4) in Logistics Corridor at 8 NYA. On Jun 19, 2019 it was discovered that approximately (b) (4) L of (b) (4) solution leaked out of the (b) (4) L (b) (4) onto the floor in the CNC Logistics Corridor (Room 1210) at 8 NYA. Because the solution was not connected nor in use with any GMP operations, there was no impact to product SISPQ. The leak was cleaned by the HAZMAT team. The root cause was that tubing seal did not maintain closure.

FRAD19E0041: On Jun 01, 2019, a leak was discovered of approximately (b) (4) L at the hose connection between the (b) (4) L bag containing (b) (4) and the transfer tubing in the (b) (4) (b) (4) row in CNC area at 8 NYA. The root cause was the connection between the (b) (4) L-bag and the transfer tubing was not fully tightened. Neither product nor process impact was identified.

FRAD19E0055: Media leak at (b) (4) L (b) (4) bag. On Jun 05, 2019, a small leak was detected during media transfer to (b) (4) L bags. The material in the leaked bag was discarded, therefore, there no impact on product and process. The root cause was a bag failure.

FRAD19E0067: Media leak from (b) (4) bag (b) (4) connection. On Jun 09, 2019 during media transfer, a small leak was detected from the manifold to the (b) (4) L (b) (4) bag (b) (4) connection. The leaking bag was isolated and sealed so there is no product impact. The root cause classification is Material Damaged/Defective as a piece of the (b) (4) that was ripped and stuck within the connection for (b) (4) #(b).

FRAD19E0080: Leak from sampling device during (b) (4) SUB sampling. On Jun 14, 2019 during the (b) (4) sampling operation from single use bioreactor (SUB) X-2200 for batch (b) (4), a small leak (1-2mL) was detected. This leak is unlikely to have any impact to the bioreactor or product SISPQ. Once the leak was detected, the sampling line was immediate clamped off using multiple pinch clamps which isolated the leak point from the bioreactor. The root cause was a defect in the sampling device.

FRAD19E0104: Leak from pump tubing insert during (b) (4) transfer. On Jun 20, 2019 during transfer and filtration of (b) (4) into the (b) (4) (b) (4) for (b) (4) Batch (b) (4), a leak of approximately 500 mL occurred on the pump tubing insert. The leak occurred upstream of the filter and all connections made to complete the transfer operation were made aseptically using new SUT; therefore, there is no impact to product SISPQ, equipment or environment. The root cause was that pump inserts were not used with the pump because of inadequate procedure.

Discussion on Leaking: Leaking is a major concern for single use technology. On Sep 01, 2020, I interviewed Mr. Kyle Bigness, Sr. Manager-(b) (4) ICB Project. All staff working with SUT require training, specifically for response to a SUT Failure. The training course "SUT Failure Response at 8 NYA (FBL-OJT-000658, Version 1.0, effective Aug 07, 2020) includes inspection on bags and line connections. The OJT material includes detailed video instructions. In the MES (eBR), Electronic Work Instruction (EWI) is available for every step in which SUT is involved. During our observation of the mock drug substance fill on Sep 03, 2020, we observed that all (b) (4) operators in the fill room are continuously monitoring the bag and tubing systems for a potential leak. As indicated in the Deviations reviewed above, all leaks in the production suite were identified in a timely manner and did not result in impacts on process performance and product quality.

Other Deviations reviewed by YXF

FRAD20E0095: (b) (4) Run for lot (b) (4) missing (b) (4) Process. On Feb 09, 2020, during review of the (b) (4) by MSAT, it was identified that the (b) (4) step following (b) (4) did not occur in the 1st PPQ run ((b) (4)). I discussed this major deviation with (b) (6), Sr. Process Engineer, Derek Pandolfo, and Matthew

Offenbacher, Quality Manager on Sep 3, 2020. The root cause was inadequate instruction in the MBR. No product impact was identified. CAPA FRAD20A0062 has been initiated in order to have the (b) (4) status updating step added to the (b) (4) ensuring that the (b) (4) status is correctly updated after the (b) (4) cleaning is performed during the (b) (4) setup recipe.

FRAD19E0212: Low (b) (4) at 8 NYA. On Jul 24, 2019, (b) (4) Batch (b) (4) exceeded the (b) (4) In-Process Control (IPC) range of (b) (4) - (b) (4), with a low (b) (4) value (b) (4) during the (b) (4). On Sep 03, 2020, (b) (6), Sr. Process Engineer, and Matthew Offenbacher provided a power point presentation on this Deviation. The total exposure time was less than (b) (4) and no impact on product was observed. The root cause was improper settings in the (b) (4) transmitter that caused the transmitter to hold a value instead of displaying the live/current value. CAPA: Settings for all (b) (4) transmitters for probes installed in (b) (4) were corrected to disable the "hold last value" mode. There have been no further reoccurrences.

FRAD20E0671: (b) (4) Control Failure at 8 NYA. On Aug 14, 2020 (growth day (b)) manufacturing attempted to start (b) (4) on SUB X-2200 after answering the (b) (4) prompt to begin. It was identified that the harvest and media supply pumps had started, but the (b) (4) of the (b) (4) were not operating as expected. The SUB (b) (4) recipe alarmed. (b) (4) were not functioning for 4 hours and 45 minutes. There was no product impact. The root cause was that an I/O connection to the (b) (4) MFCs was disconnected. After reconnecting the I/O cable the (b) (4), media and harvest pumps were successfully started.

FRAD19E0365: (b) (4) result outside of comparability protocol FBL-RPT-000447 per FBL-MTD-000049. On Aug 22, 2019, QC Chemistry was notified that the (b) (4) result (b) (4) (round to (b) (4)) mol/mol for (b) (4) lot (b) (4) was outside of the comparability range of (b) (4) - (b) (4) mol/mol per FBL-RPT-000447, *"Comparative Analytical Assessment Study Protocol for* (b) (4) *ICB Process PPQ Run at 8NYA Facility"*. The root cause was identified as assay variability. During a discussion with Ms. (b) (6), Molecule Steward Principle, and Ms. (b) (6), Sr. Scientist on Sep 3, 2020, I noted that (b) (4) (b) (4) index measured with AA glycosylation were also lower compared to other batches, therefore this outside of comparability result might not be due to assay variation per se. They agreed with my comment. I emphasized that root cause analysis should be more thorough and critical.

FRAD19E0169**:** Campus Wide Network Outage Impacting (b) (4) at 8 NYA. This deviation occurred on Jul 10, 2019 because a net switch failed to operate as intended. The switch was replaced. No impacts on preprocess and product were identified.

FRAD19E0193: Campus Wide Network Outage Impacting (b) (4) and (b) (4) (45, 51, 74, 76, and 80 NYA) Manufacturing systems. This deviation is associated with FRAD19E0169 described above. On Sep 2, 2020, Mr. Navin Tiwari provided an overview of the network system

in the facility. He clarified that the network outage that triggered these two deviations only impacted data transfer and not the process control, with no GMP data loss.

FRAD19E0221: Atypical formulated bulk protein concentration result for Lot (b) (4). This deviation occurred on Jul. 28, 2019. During manufacture of PPQ Batch (b) (4), an atypical protein concentration of (b) (4) g/L was measured for Formulated Bulk ((b) (4) by the manufacturing facility. This sample was retested by the QC Laboratory. After comparing the results measured at the manufacturing facility and the QC laboratory, the root cause was determined to be the assay performed at the manufacturing facility. There is no pact on product quality. A CAPA was taken to improve the assay performance.

No objectionable observation was identified.

Annual Product Review, Internal Audits and Contract Agreements

This section was written by WS

On 31 August 2020, Mr. (b) (6) provided an overview of the internal audit process owned by Quality and tracked within the validated Phenix application. I reviewed BQ-OOP-00026, *"Self-Inspection"*, v7, Effective date 14/07/2020. The self-inspection process is according to schedule that includes a risk assessment, with each area of manufacture inspected a minimum of (b) (4). Self-inspections are current, with the process paper based. Individuals supporting the self-inspection process are trained. In the event an objectionable condition is observed during the self-inspection process, (b) (4) are allowed for correction of the objectionable condition and report. QA reviews the report and response to any objectionable condition.

I reviewed product quality review under FBL-SOP-000424, *"Product Quality Review Procedure for Framingham Biologics"*, v6 Effective Date 25/03/2020. A product quality review is conducted annually according to schedule for each product, with the process comprehensive. Quality reviews are current, with a report generated that is approved by quality.

On 1 September 2020, Ms. Melissa DiTullio, Associate Director Compliance Auditing provided an overview of contract agreements. I reviewed BQ-GOP-000002, *"Supplier Management"*, Effective date 03/01/2020. There are three types of categories for quality agreements based on types of suppliers: Category 1 and 2 for applications that have a direct impact on the quality of the product that includes test labs, calibration services, recall and passivation. Category 2 originally only required a manufacturing quality review, with Category 3 for off the shelf non product impact suppliers. Contract agreements are reviewed (b) (4) according BQ-GOP-000008, *"Quality Agreements"*, v5, Effective date 21/05/2019, with quality agreements managed through the (b) (4) facility. Quality agreements are generated according to approved template, with the supplier template sometimes used as long as the minimum requirements are present with Sanofi legal review.

On 03 September 2020, Ms. Melissa DiTullio, Associate Director Compliance Auditing, Mr. (b) (6), Quality Engineer Principle, and Mr. (b) (6), Quality Auditor Principle provided a follow up to the quality agreements, with 5 past due. Per BQ-GOP-00008, *"Establishing and Maintaining Quality Agreements"*, v5, Effective date 21 May 2019, Quality Agreements should be reviewed within (b) (4). Three of the quality agreements did not have CAPAs. I (WS) questioned if the deficiency was related to COVID-19, with the firm indicating no. The firm indicated that the past due quality agreements would be identified as late in the annual PQR, with the current quality agreements remaining in effect until reviewed. There is no product quality impact, but I reminded the firm about complying with expectations according to procedure.

Reference Discussion Item WS-5 in Section XII, GENERAL DISCUSSION WITH MANAGEMENT.

Product Complaint and Return Procedure

This section was written by WS

On 01 September 2020, Ms. Julie Kelly, Director of Quality and Mr. Matthew Offenbacher, Quality Manager provided an overview of the complaint process according to SOP-BQ-GOP-00065, *"Genzyme Global Product Event Management Procedure"*, v9, Effective date 25/08/2020. The procedure is a corporate directive, with complaint intake by call center that includes pharmacovigilance, and customers. A form is used to capture information on the complaint. The complaint investigation process includes determining if the complaint is valid or invalid, with valid complaints potentially including a BPDR and/or field alert report. Complaints are trended and can be expanded to other products. Feedback is provided to the complaint source.

On September 2020, Mr. (b) (6), Senior Material Support Specialist, Mr. Manpreet Bai, Director of Quality, and Mr. (b) (6), Senior Manager Materials Operations provided an overview of the return procedure under NBO-SOP-000051, *"Receipt of Materials at the Framingham and Northborough Facilities"*, v12, Effective date 03/06/2020. Returns include finished goods and raw materials, with five different scenarios.

1. Material not making it the distribution site but under Genzyme control are returned under procedure NBO-SOP-00341. A deviation investigation is conducted with confirmation that the material was maintained under proper temperature with quality review before release.
2. Return of material from the market place is managed under NBO-SOP-000264. This is product returned from a patient, with the product always destroyed.
3. Product returned based recall, market withdrawal is conducted under NBO-SOP-00084. The product may be destroyed based on investigation and guidance from the recall team that includes quality.

4. Returned product from distribution center under Sanofi control is performed under transfer order. In this situation, product could be relabeled for other countries based on demand, with the process conducted according to procedure and under QA control.
5. Transfer of raw material from other manufacturing sites is according to procedure, with the raw materials under Genzyme control. Chain of custody is maintained.

In all cases, the returned product is quarantined and secured pending disposition.

No objectionable observation was identified.

Change Control Procedure and Change Controls

This section written by WS

On 01 September 2020, Ms. (b) (6), Quality Engineer Principle, Mr. Jason Fahy, QC Associate Director, Mr. Patrick Wells, Associate Director QC Science and Technology, Mr. (b) (6), Project Analysts Principle, Mr. (b) (6), Manufacturing Specialist III, and (b) (6), Senior Manager Manufacturing provided an overview of the change control process. I reviewed SOP BQ-GPO-000175, *"Phenix Change Control Process"*, v11, Effective date 06/08/2020. The scope of the procedure is a global operating procedure for change control. Change control are from Level 1 to 3.2, where 3.2 requires regulatory and QA input. The process for change control includes a management discussion that includes QA and other impacted departments, quality person assigned if the change is approved, GEMBA, and risk assessment. Change controls are management in the validated application Phenix, with the workflow for change created. Hierarchy approval includes the affected department manager, site coordinator QA assignment, expert evaluation, site coordinator QA final approval and change plan, regulatory and quality impact assessment when required. Change work actions are conducted with conclusion, followed by site coordinator and decision for closure. Effectiveness checks are conducted for changes impacting the manufacturing process. I reviewed the following change controls:

- Change Control 2019 FRACC0009: Implementation of 68 NYA 2nd floor laboratory for QC (b) (4) ICB testing, level 2 change control. Drug substance analytical testing was implemented in 2019 that included equipment qualification, validation and methods. This was part a prior regulatory submission.
- Change Control 314067. New method enrollment for (b) (4) 8 NYA ICB that includes raw materials and disposables. The change control supported the addition of raw materials and disposables into SAP (Athena).
- Change Control 322866. Addition of intermediate solutions, specifications in Athena.

No objectionable observation was identified.

Stability

This section written by YXF

On August 31, Ms. Kimberly Cheung, Senior Director-Stability and Statistics provided an overview of the (b) (4) DS stability program. I reviewed FBL-PTM-000060, *"Stability Protocol for* (b) (4) *DS"*, v4.0, Effective date 07/29/2020, which governs the stability study at the firm. The stability samples (PN (b) (4)) were stored in (b) (4) Bags at 6 -10 °C over 4 months or at 25±2°C/60±5%RH over 4 weeks. For each stability study approximately (b) (4) mL of sample is filled into each of (b bags ((b) (4) % capacity). These are small-scale representations of the production storage containers, mimicking primary product contact and incidental contact materials. Testing windows are (b) (4) and (b) (4) for long-term and accelerated storages conditions, respectively. All stability results for the PPQ batches were with in the stability specification and there were no significant trends.

There were no stability samples at storage during the time of inspection.

No objectionable observation was identified.

Recall

This section was written by WS

On 31 August 2020, Mr. (b) (6) , Principle Quality Engineer provided an overview of recalls, conducted according to FBL-SOP-00109, *"Recall Management for Framingham Biologics Site"*, v4, Effective date 13/03/2020. Conditions that can cause a recall are a critical deviation, customer complaint, adverse event, stability failure and regulatory request. A recall event is determined by corporate quality, with a recall team assembled according to procedure FBL-SOP-00109 that includes a deviation investigation managed within the validated Phenix application. The location of the product for recall is determined by materials management, with on-site remaining product determined through Athena (SAP), electronically quarantined and locked from distribution. Product reconciliation is performed, with other associated products accessed in the recall. There have been no recalls in the last 4 years. In the event there is no recall, an (b) (4) mock recall is performed.

No objectionable observation was identified.

Document Control Procedures

This section written by WS

On 31 August 2020, Ms. (b) (6) , Principle Quality Documentation provided an overview of the document management system under validated application Geode+ for creation, revision and obsolescence of documents, owned by Quality Systems. I reviewed document BQ-GOP-000181,

"Geode+ Controlled Document Lifecycle", v9, Effective date 25/08/2020. The process includes the creation of a document (draft) that is placed within a workflow for review and edit, followed by approval. The document is trained upon in the validated learning management system, where 100% of training must be conducted prior to becoming effective. The revision process for an existing procedure is the same as prior. All procedures that include SOPs and work instructions are on-line, no paper, with the validated application for read and understand Gibraltar, a read only backup of Geode+ effective documents.

No objectionable observation was identified.

Computer Systems

This section written by WS

On 01 September 2020, Ms. Patricia Hebert, Senior Process Engineer 1 provided an overview of data integrity. I reviewed FBL-PRD-000013, *"Data Integrity Program for Framingham Biologics"*, v1. The prior is based on QS-107-08, *"Implementation of Corporate Systems and Computerized Equipment"*, Effective date 06 September 2017. A key element is the configuration of systems that is documented, allowing for system restore, with computerized systems (equipment, infrastructure and software) qualified/validated. User access to systems is governed by personnel ownership of their unique User I.D. and Password, with access to computerized systems managed during personnel onboarding and off boarding. The review of system audit trails, GMP data is conducted by IT based on risk, with audit trails including time, date stamp and person responsible for activity. Audit trails are prohibited from deletion, with the audit trail archived with the source data. A GAP analysis has been conducted for Production, QA and Laboratory Systems, with no GAPs identified. In security of data, data may be paper based on system limitations, with electronic data not available for deletion or change. In validation of applications, a loop check is conducted. Data generated by an operator is reviewed by an independent secondary reviewer, with audit trail review that includes review during batch release. The ability to retrieve data from system is tested periodically. (b) (4), data is transferred (back-up) to a qualified validated secure server.

On 01 September 2020, Navin Tiwari, Director ITS and Automation, Ms. Patricia Hebert, Head of Quality - Digital/Data Compliance, Mr. Christopher Blackburn, Director QA ICB (b) (4), Ms. (b) (6), Process Engineer III, Mr. (b) (6), Senior Quality Engineer, Mr. (b) (6), Senior Manager Manufacturing, Mr. Dean Morris, Autonomous Production Unit Head, and Ms. Kate LaRoche, Manager Quality provided a follow up to quality critical alarms associated with upstream and downstream manufacture. Regarding the (b) (4) liter bioreactor, a physical loop check was conducted back to (b) (4), along with the SCADA alarm and visual indicator. Alarm data progresses to pi (the data historian server) and Werum, the batch record application. ANMS, the alarm notification management system that is linked to (b) (4) both validated, was also checked for alarm loop check. QA as part of batch release reconciles the ANMS alarms to Werum. I reviewed FBL-SOP-001320, *"Inova (Werum) Execution at 8 NYA"*, V2, Effective date 24/05/2019 for alarm reconciliation. Section 6.83 for

manufacturing and 6.8.4 for QA identified the quality critical alarm reconciliation ANMS to Werum.

No objectionable observation was identified.

Facilities and Equipment

A. Facilities

HVAC, HEPA Filters and BMS

This section written by WS

On 01 September 2020, Mr. (b) (6), Senior Facility Manager and Mr. (b) (6) Senior System Engineer Utilities provided an overview of HVAC systems for 8 NYA consisting of a main (b) (4) unit that includes (b) (4) There are (b) other air handling system: (b) unit upstream, (b) unit downstream and CNC space, with the unit's recirculation in design. The range of (b) (4) air is (b) (4) to (b) (4) % based on AHU and pressure requirements. The individual units contain (b) (4) and terminal HEPAs. The pre-filters are replaced and not cleaned. Preventive maintenance is performed internally according to schedule (b) (4) as determined by the liability management department. Ceiling HEPAs are certified (b) (4), with the BMS system monitoring system performance for airflow and temperature that is alarmed, with call out notification in the event of an aberrant condition.

On 02 September 2020, Mr. (b) (6), Metrology Physical Testing Group Lead provide an overview of HEPA certifications according to procedure FBL-SOP-000698, *"Certification of HEPA Filter"*, v4, Effective date 03/06/2020. Ceiling HEPAs are certified (b) (4), with LFCB (b) (4), with the certification process conducted internally using a photometer. The scan process is (b) (4). There is no expiration for the HEPA filters for replacement according to the filter manufacturer, with filters taken to failure. In the event of a filter leak, the filter can be patched with patch log, with replacement of the filter preferred.

On 04 September 2020, Ms. Patricia Hebert provided an overview of the BMS, a non-GxP systems limited in use to field devices, air-handling systems used in a non-GxP application. EMS is the GMP application for monitoring that includes manufacturing suite differential pressures. I reviewed the protocol for the installation and operational qualification for the environmental monitoring system (EMS) at 74 NYA per CCR#62776. The IQ was standard with a third party certification of the system for GMP compliance. An upgrade of the system occurred for interface functionality according to VP-300 33, *"Corporate System Testing and Decommissioning Use Test Scripts at Framingham"*, Effective date 07 April 2016. A loop check was conducted from EMS, pi and ANMS, with results acceptable. I reviewed the periodic review of computerized systems according to CSV FBL-SOP-000957, *"Procedure for Periodic*

Review of Computerized Systems", v3, Effective date 01/01/19. Computerized system are reviewed (b) (4) by paper review to assure the qualified validated state remains unchanged. Furthermore, I reviewed FBL-SOP-000687, *"IT Compliance Verification"*, v7, Effective date 30/03/20, with IT reviewing audit trails, personnel access, etc. (b) (4) that includes backup and restore capability.

I reviewed the periodic review for EMS under IS-1604585, *"2019 Periodic Review Report for 006 EMS Framingham,"* January 2020. The review was comprehensive. I reviewed FLB-SOP-000930, *"Management of Computer Systems and Infrastructure"*, v5, Effective date 27/11/2019 as it pertains to hardware and software version control. Applications migrate from development to validation/production. In validation, all non-conformances must be satisfied, with different controls for different systems. For backup and restore, the current version is known base on IT file designation, with (b) (4) contracted as a tape depository for systems.

No objectionable observation was identified.

Water (Pre, PW and WFI) and (b) (4)

This section written by WS

On 02 September 2020, Ms. Jaclyn Blaisdell, Associate Director - Commissioning, Qualification and Validation, Mr. Foster Malcom, Associate Director Manufacturing Engineering, Mr. Robert Lavallee, Quality Engineering Principle, and Mr. (b) (6), Maintenance Group Lead provided an overview of the qualification for the water for injection system. I reviewed FBL-RPT-000637, *"8 NYA Framingham Manufacturing Quality Trend Report Critical Utilities"*, (b) (4), v1, Effective date 20/12/19. The report included water, (b) (4) and (b) (4) testing. WFI testing started in April 2019, with (b) (4) points of use tested (b) (4) for bioburden, endotoxin, TOC, conductivity and nitrates. The (b) (4) data for bioburden was acceptable, with endotoxin having 9 alert level excursions, points of use (b) (4) and (b) (4). The locations are at the WFI supply to the storage tank from the (b) (4). The initial root cause was non-classified air migrating into the open WFI transfer line to the storage tank from the (b) (4), transfer line to drain. The drain isolation valve was reconfigured to be closed post WFI manufacture, with the transfer line now sanitized (b) (4). It was determined that the actual primary root cause of the endotoxin was from the pre-treatment system, (b) (4), with sanitization by (b) (4) changed from (b) (4) to (b) (4). Water pretreatment system management is conducted internally. There is currently no routine testing of the pretreatment system to assure system performance, with the exception of an engineering protocol, with a change control initiated for routine testing (19FRACC0032), frequency to be determined. I reviewed the (b) (4) (b) (4) WFI system testing for with some hits for TOC.

I reviewed the (b) (4) WFI data under FBL-RPT-000732, *"8 NYA Framingham Manufacturing Quality Trend Report Critical Utilities* (b) (4). Testing for bioburden, endotoxin, nitrates, conductivity was acceptable, with some alert level hits for TOC. It was further discussed that

WFI must meet the conductivity specification before water is sent to the storage tank from the (b) (4).

I reviewed the (b) (4) WFI data under *"8 NYA Framingham Manufacturing Quality Trend Report, Critical Utilities"*, (b) (4). There were 4 bioburden alert and 1 action level excursion that included points of use (b) (4) and (b) (4). An engineering change was made that included longer point of use flush and (b) (4). Furthermore, there were TOC alert and action level excursions.

I reviewed the (b) (4) WFI trend data under FBL-RPT-000911, *"8 NYA Framingham manufacturing Quality Trend Report"*, Critical Utilities, (b) (4), v1, Effective date 25/06/2020. There was 1 alert and 1 action hit for TOC and bioburden, with 4 action level excursions for endotoxin at the tank supply from (b) (4).

The firm provided a summary of (b) (4) water data, with some TOC excursions alert and action level, and 1 alert level excursion for bioburden. On line TOC data for supply and return was acceptable, with the elevated TOC levels in the water confirmed as (b) (4) by third party laboratory June 2020.

I reviewed CAPA in mitigation of the false positive TOC failures, with a CAPA from February 2019, completed 2020 for how samples are taken in mitigation of contamination with (b) (4). The process for sampling includes acquisition of the TOC, conductivity and nitrate samples, followed by (b) (4) application to the sample port and acquisition of the bioburden and endotoxin sample. An additional CAPA FRAD19A0094, Opened October 21, 2019, Closed February 14, 2020 suspected the use of (b) (4) as the cause of the false positives, with a focus on sampling technique. CAPA FRAD20A0315 opened August 18, 2020 supports training for sample acquisition consistency and FRAD20A316 for time for WFI dispense, limited (b) (4) application and process for sanitization of gloves. Both CAPAs were initiated based on adverse trends in TOC. In discussion with the firm, the false TOC positives are mainly at the alert level. The use of an attachment to sample ports to reduce flow in support of sample acquisition may be a contributing factors in the TOC excursions, with the attachment under review.

Reference Discussion Item WS-3 in Section XII, GENERAL DISCUSSION WITH MANAGEMENT.

On 04 September 2020, Mr. Foster Malcolm, Associate Director of Manufacturing Engineering provided a follow up for the WFI (b) (4) to tank transfer line and reconfiguration of the valve to drain. In a review of the change, WFI is piped to the storage tank from the (b) (4), with the valve for divert water to drain (until acceptable conductivity level) originally open, but now closed. The original system design never supported the draining of the WFI transfer line completely to low point, with the valve configuration change acceptable.

The firm provided follow up for the pretreatment system, with (b) (4) data indicating low levels of endotoxin at the WFI inlet from the (b) (4), with endotoxin carryover from the pre-

treatment system as determined from FRAD19E0495, opened November 2019, closed June 2020. An engineering protocol that included sampling, identified elevated levels of endotoxin from the (b) (4) June 2019 and May 2020, with CAPA FRAD20A0220 changing the sanitization frequency from (b) (4) to (b) (4). On 03 September 2020, the firm provided follow up on the engineering protocol implemented August 24, 2020, with (b) (4) sampling from (b) ports: (b) (4) Testing at the (b) (4) valves post (b) (4) and prior to the WFI entering the tank indicated the absence of detectable levels of endotoxin. A change control has been implemented for (b) (4) routine testing of the pretreatment system in support of assuring system performance.

Reference Discussion Item WS-4 in Section XII, GENERAL DISCUSSION WITH MANAGEMENT.

I reviewed the qualification for the (b) WFI (b) (4) under document F008-ED-IQ-0009, *"Installation Qualification and Final Report for the WFI Generator* (b) (4) *at 8 NYA, Framingham Biologics, F008-WFI-101, F008-WFI-102"*, Effective date 19 April 2018. The IQ was standard in design with the system supported by (b) distribution loops, with a (b) (4) (b) (4) at the outfeed from the tank, with sanitization performed (b) (4).

I reviewed the OQ F008-ED-OQ-0016, *"Operational Qualification and Final Report for the WFI* (b) (4) *System at 8 NYA, Framingham Biologics F008-WFI-101 and F008-WFI-102, WFI* (b) (4) *"*, Effective date 20 June 2018. The OQ was standard in design and acceptable.

I reviewed the distribution system IQ, *"Installation Qualification and Final Report for the WFI Storage and Distribution System at 8 NYA Framingham Biologics F008-WFI-103"*, Effective date 10 May 2018. The IQ was standard in design and covered (b) (4) loops.

I reviewed the OQ for the distribution loops under F008-ED-OQ-0017, *"Operational Qualification Final Report WFI Storage and Distribution System at 8 NYA Framingham Biologics, F008-WFI-103"*. The OQ was standard in design and acceptable. I reviewed the amendment to the OQ F008-WFI-103, F008-ED-OQ-0017a1, *"Amendment # 1 to the Operational Qualification and Final Report for the Water for Injection Storage and Distribution System at 8 NYA*", Framingham Biologics. The amendment was for loop sanitization and vent filter for storage tank integrity. Testing was acceptable.

I reviewed the PQ for the WFI system that consisted of Phase 1 for (b) (4), (b) (4) use points tested (b) (4); Phase 2 testing for (b) (4), same as prior; and Phase 3 routine testing. Testing included bioburden < (b) (4) CFU/100 mL, conductivity per USP, TOC ≤ (b) (4) ppb, endotoxin < (b) (4) EU/mL, and nitrates ≤ (b) (4) ppm, with testing to specification.

(b) (4): The (b) (4) is sampled at (b) (4) points of use (b) (4), with the generator sampled (b) (4) for endotoxin, TOC, nitrates and conductivity. I reviewed the (b) (4) trend data, with 1 alert excursion at the generator for endotoxin and TOC, resample acceptable. I reviewed the (b) (4) and (b) (4) and (b) (4) data, all testing acceptable.

It was further explained that post water pre-treatment system, the water passes through a (b) (4) (b) (4), with direct feed to the WFI (b) (4). (b) (4) is generated from (b) (4).

I reviewed the (b) (4) generator IQ under F008-ED-IQ-0006, *"Installation Qualification and Final Report for* (b) (4) *Generator and Distribution System at 8 NYA Framingham Biologics F008-CSG-100"*, Effective date 14 March 2018. The IQ was standard in design and acceptable. I reviewed the OQ under F008-ED-OQ-0015, *"Operational Qualification and Final Report for* (b) (4) *Generator and Distribution System at 8 NYA, Framingham Biologics F008-CGS-100"*, Effective date 10 May 2018. The OQ was standard in design and acceptable. I reviewed the PQ, with (b) (4) testing performed at the generator, (b) (4), WFI storage tank, and (b) (4) under F008-CSG-100, *"Performance Qualification and Final Report for* (b) (4) *Generator and Distribution System at 8 NYA, Framingham Biologics"*. Testing was conducted for (b) (4) intervals that included appearance, conductivity, TOC, endotoxin and nitrates to WFI quality specifications. Test was to specification and acceptable.

Reference Discussion Item WS-3 and 4 in Section XII, GENERAL DISCUSSION WITH MANAGEMENT.

(b) (4)

This section written by WS

On 01 September 2020, Ms. Jaclyn Blaisdell, Associate Director - Commissioning, Qualification and Validation, Mr. Foster Malcom, Associate Director Manufacturing Engineering, Mr. Robert Lavallee, Quality Engineering Principle, Mr. (b) (6), Senior Facilities Manager, and Mr. (b) (6), Quality Engineering provided an overview of (b) (4). I reviewed the IQ for the (b) (4) system under F008-(b) (4)-005, *"Installation Qualification and Final Report for* (b) (4) *System at 8 NYA, Framingham Biologics"*, Effective date 30 Oct 2018. The system is (b) (4) for GMP suite penetration, with the IQ standard in design. I reviewed the OQ under document F008-ED-OQ-0003, *"Operational Qualification and Final Report for the* (b) (4) *System at 8 NYA Framingham Biologics, F008-*(b) (4)*-105"*, Effective date 15 March 2018. System design includes a (b) (4) I reviewed PQ 25-0005P, *"PQ and Final Report for the Process* (b) (4) *System at 8 NYA, Framingham Biologics, F008-*(b) (4)*-105"*, Effective date 10 September 2020. The system has no (b) (4), with (b) (4) sites of use that are (b) (4). Testing was for (b) (4) at (b) (4) point of use that included moisture, ≤(b) (4) °C; Hydrocarbon, ≤(b ppm; Non-viable to room classification; Viable, ≤

(b) (4) CFU/1000 liters and mold ≤(b CFU/1000 liters, and Grade A use <(b CFU/1000 liters. All testing was acceptable.

I reviewed the IQ for the (b) (4) system under protocol F008-IQ-005, *"Installation Qualification and Final Report for* (b) (4) *System at 8 NYA Framingham Biologics, F008-*(b) (4)*-106"*, Effective date 30 October 2018. The IQ was standard with construction (b) (4) for GMP suite penetration. There is no (b) (4), with (b) (4) performed at points of use. I reviewed the OQ under F008-ED-OQ-0004, *"Operational Qualification (OQ) and Final Report for* (b) (4) *System at 8 NYA, Framingham Biologics"*, 07 March 2018. The OQ was standard in design and acceptable. I reviewed the PQ under PQR-02-8 NYA-CQ-0003, *"Performance Qualification Report (25-0007P) for 02-8NYA-CQ-0003 F008-*(b) (4)*-106"*. (b) (4) of testing was conducted for (b) points of use, with dew point at ≤(b) (4) °C, hydrocarbon ≤(b) (4) ppm, and viable <(b) (4) CFU/1000 liters (mold ≤(b) (4) CFU/1000 liters). Non-viable testing was not tested based on hazard (ignition) concern. All testing was acceptable.

I reviewed the IQ for (b) (4) distribution system under *"Installation Qualification and Final Report for Process* (b) (4) *System at 8 NYA, Framingham Biologics"*, F008-(b) (4) -100, 30 October 2018. The IQ was standard in design, with system having no tank (b) (4), with (b) (4) at points of use. Construction is (b) (4) for GMP suite penetration. I reviewed the OQ under F008-ED-OQ-0008, *"Operational Qualification and Final Report for Process* (b) (4) *at 8 NYA Framingham Biologics F008-*(b) (4)*-100"*, Effective date 20 July 2018. The OQ was standard in design and acceptable. I reviewed the PQ under *"Performance Qualification and Final Report for the Process* (b) (4) *System at NYA, Framingham Biologics at 8 NYA Framingham Biologics F008-*(b) (4)*-100"*, Effective date 10 September 2018. Testing for the (b) (4) points of use was conducted over (b) (4) for dew point, ≤(b) (4) °C; Hydrocarbon, ≤(b) (4) ppm; Non-viable to room classification; and viable <(b) (4) CFU/1000 liters (<(b) (4) mold). All data was acceptable.

I reviewed the IQ for (b) (4) system under *"Installation Qualification and Final Report for* (b) (4) *System at 8 NYA, Framingham, Biologics, F008-*(b) (4)*-101-103"*, Effective date 17 April 2018. The system is (b) (4) for GMP suite penetration, with the IQ standard in design. I reviewed the OQ under F008-ED-OQ-0007, *"Operational Qualification and Final Report for* (b) (4) *System at 8 NYA, Framingham Biologics F008-*(b) (4)*-101, F008-*(b) (4)*-103"*, Effective date 01 June 2018. The OQ was standard in design. I reviewed the PQ under *"Performance Qualification Final Report for* (b) (4) (b) (4) *System at 8 NYA, Framingham Biologics at 8 NYA, 25-0004FR"*, v1. (b) (4) (b) (4) of testing was conducted for (b) (4) points of use with moisture ≤(b) (4) °C; Hydrocarbon, ≤(b) (4), ppm; Non-viable to room classification; and viable, ≤(b) (4) CFU/1000 liter (mold <(b) (4)). Testing was acceptable. There was an IQ amendment, extra valves at main (b) (4) for future expansion of the system, acceptable.

On 02 September 2020, I reviewed the final report for the compressors under *"Installation and Operational Qualification and Final Report for* (b) (4) *System at 8 NYA, Framingham Biologics F008-ED-IQ-0008al. F008-*(b) (4)*-101, and F008-*(b) (4)*-103"*, v1. Test was acceptable.

I reviewed the summary of testing for (b) (4) . (b) (4) point of use on the (b) (4) (b) (4) system is tested (b) (4) , with the (b) (4) tested (b) (4) . Testing (b) (4) (b) (4) is for dewpoint, hydrocarbon, non-viables and viables, with testing from (b) (4) to (b) (4) (b) (4) acceptable. In (b) (4) , there was an additional PQ completed for work performed in support of future expansion of the system, with testing for the complete system acceptable. I reviewed the (b) (4) trend data, there was 1 hydrocarbon failure with retest acceptable. Testing represented (b) (4) .

I reviewed the testing for the (b) (4) system that included dew point, non-viables, viables, total particles and hydrocarbon, with testing for (b) (4) and (b) (4) acceptable. No further testing was performed until (b) (4) , testing acceptable, with system out of service for future expansion work.

I reviewed the (b) (4) testing that included hydrocarbon, viable, non-viable and dewpoint, with (b) (4) (b) (4) acceptable. There was no testing for (b) (4) and (b) (4) and (b) (4) future expansion work. The (b) (4) test data indicated 1 non-viable excursion. Remedial action included (b) (4) , (b) (4) change out, passivation for the sample port that failed. A borescope identified particles, with resampling after corrective action acceptable.

I reviewed the (b) (4) testing that included dew point and viables, with testing for (b) (4) acceptable, with no testing for (b) (4) and (b) (4) and (b) (4) based on future expansion work. The (b) (4) data was acceptable.

No objectionable observation was identified.

Environmental Monitoring (EM) and Facility Cleaning (Efficacy)

This section written by WS

On 03 September 2020, Mr. (b) (6) , Quality Engineer Principle and Sean O'Brien, Director of Quality Contamination Control provided an overview of the environmental monitoring for the facility. I reviewed the "*Final Report for Environmental Qualification of the 8 NYA* (b) (4) *Biologics Manufacturing Facility (* (b) (4) *)*", 14 August 2019 Doc 25-0003FR-R2 Lal 25-00003FR. The site procedure for environmental qualification is based on ISO 146641-1, with static testing for (b) (4) . The report is for Grade C and D space, with Grade A under a different report. Testing included the following with acceptance criteria to USP and ISO:

Test	Grade C Specification	Grade D Specification
Non-viable 5 and 0.5 micron	To room classification	To room classification
Viable (b) (4) liters Sampled	Alert (b) (4) , Action (b) (4)	Alert (b) (4) , Action (b) (4)
Viable Surface, Work Surface	Alert (b) (4) CFU, Action (b) (4) CFU	Alert (b) (4) CFU, Action (b) (4) CFU
Viable Surface, Floor	Alert (b) (4) CFU, Action (b) (4) CFU	Alert (b) (4) CFU, Action (b) (4) CFU

CNC space has no environmental monitoring.

I reviewed the (b) (4) of static testing from (b) (4) to (b) (4), with staggered testing per area in support of lab testing. Viable air alert (mold) recoveries were identified in Room 1312, janitors' closet. The area contains no HEPA filtration, with cleaning and adjustment of the door louvers conducted, with the retest acceptable. Room 1223 (Grade D) had a (b) (4) viable surface alert level excursion, (b) (4) CFU/25cm^2, with no corrective action taken. (b) (4) (b) (4) testing was acceptable. Room 1360 (Grade D) personnel (b) (4) had door handle alert level excursions for (b) (4) mold. The root cause was gloves. Room 1350 (Grade D (b) (4) Personnel) had 3 CFU, 2 of which were mold and 1360 (Floor Surface), (b) (4) CFU, (b) (4) and (b) (4) (b), respectively. Subsequent sampling was acceptable, with static testing acceptable.

I reviewed the dynamic testing for (b) (4), with (b) (4) to (b) having more alert and action level excursion than expected. A pause in testing occurred at (b) (4) to assess root cause, with the root cause cleanroom behavior, with behavior adjusted as it pertains to operational readiness, non-GMP to GMP. 16 Grade D and C excursions, 2 viable at alert and action level and 14 surface plates, 6 alert and 8 action were identified, with the root cause remediation work in the area. Testing resumed at (b) (4), with 4 alert and 1 action for Grade D space, with no trend. Routine cleaning was conducted during the testing period.

I reviewed the disinfection procedure for the cleanroom under work instruction *"Facility and Equipment Disinfection FBL-EWI-00005"*, v2. Disinfection of the facility includes (b) (4) (b) (4) cleaning of floors, Grade C space and all material and personnel (b) (4) that includes janitor's closets. (b) (4) into drains is also performed, with weigh and dispense Room (b) (4) floors cleaned. (b) (4), (b) (4) cleaning of floors is conducted in Grade D space, with the exception of weigh and dispense. (b) (4) cleaning a walls is performed that includes ancillary equipment, interior of gown hampers, and trash receptacles. (b) (4) (b) (4) sporicidal cleaning of the facility is performed. CNC space includes a (b) (4) cleaning of floors, gowning only, with (b) (4) cleaning of ancillary equipment, hampers and storage areas, floors, with (b) (4) of cubes for shoes. CNC (b) (4) cleaning includes (b) (4) of prior with sinks, floors and drains. (b) (4) cleaning includes ceiling. Return to service cleaning includes (b) (4), and (b) (4) cleanings for all controlled space.

I reviewed cleaning efficacy under FBL-RPT-001032, *"Disinfection Efficacy Studies for the Framingham Bioprocessing Campus 2020"*, Effective date 02/09/2020. The sanitization cleaning agents evaluated were (b) (4) . (b) (4) are used at 8 NYA with (b) (4) for Equipment. (b) (4) is applied in general cleaning, with (b) (4) applied (b) (4). Evaluated were gram positive and negative organisms, spores and mold that included facility isolates. 5 substrates consisting of (b) (4), glass, (b) (4) were tested, with a 3 log reduction for bacteria and mold and a 2 log for spores. (b) (4) replicates were performed for each substrate, with (b) (4) on to the substrate with organisms. The cleaning agents were applied by (b) (4), with (b) (4) requiring a wipe of the surface with the cleaning agent to achieve the

desired log reduction. Wiping is consistent with how the cleaning agent is applied in commercial manufacture, with the contact time for (b) (4); (b) (4); and (b) (4). After sanitization, the residual cleaning agent is removed with (b) (4).

I reviewed the EM data for (b) (4) under *"8 NYA Framingham Manufacturing Quality Trend Report, Environmental* (b) (4) *FBL-RPT-000626"*, v1, Effective date 08/01/2020. I reviewed the Grade C EM with no alert or action level excursions, with Grade D space having 12 action level excursions for surface viables. The root cause was passivation equipment brought into the facility that was not adequately sanitized based on design. Additional cleaning using (b) (4) was performed, with EM acceptable. Furthermore, viable air in Grade D space had 5 alert level excursions, with resample acceptable. Total particle for Grade C and D space was acceptable.

I reviewed the (b) (4) *"8 NYA Framingham Manufacturing* (b) (4) *Trend Report, Environmental Monitoring* (b) (4) *, FBL-RPT-000731"*, v1, Effective date 26/03/20. The trend data was only partial, with a (b) (4) until March 2020. There were some Grade C and D alert excursions, with retest acceptable.

I reviewed the (b) (4) *"8 NYA Framingham Manufacturing* (b) (4) *Trend Report, Environmental Monitoring* (b) (4) *FBL-RPT-000912"*, v1, Effective date 25/06/20. There was no Grade C monitoring based on (b) (4). I review the Grade D EM with no alert or action level excursions.

I reviewed the (b) (4) Interim Report, with 2 alert and 1 action in Grade D space gowning. Resample was acceptable.

No objectionable observation was identified.

Pest Control

This section written by WS

On 01 September 2020, Mr. (b) (6), Senior Facilities Manager and Mr. (b) (6) (b) (6), Facilities Specialist provided an overview of pest control according to SOP-FBL-SOP-000512, v5, Effective date 29/05/2020. Pest control is contracted to a certified pest control company (b) (4), with the firm on-site (b) (4) or as required. Bait traps are placed around buildings, with bug lights at doors and small trap stick mats at other locations. Insecticide is not allowed within buildings. A report of finding by (b) (4) is provided each visit with trending. In the event of pest incursion into the GMP suite, the process includes notification of maintenance and the pest placed within a container. The area where the pest was located is cleaned with (b) (4); (b) (4) contact time, with deviation investigation initiated. I reviewed the (b) (4) and (b) (4) pest control data, with no negative trends.

On 03 September 2020, Ms. Kate LaRoche, Manager of Quality provided a follow up for pest incursions into the GMP suite. There have been minor excursions, with pest control program adequate.

No objectionable observation was identified.

B. Equipment

Maintenance (Preventative Maintenance (PM), Calibration & Equipment Logbooks)

This section written by WS

On 01 September 2020, Mr. Brain Donohue, Associate Director of QC Microbiology provide a follow up to logbooks, with logbook review conducted according to FIL-SOP-000942, *"Good Documentation Practices"*, v6, Effective date 01/09/2020. Under Section 6.10.9 of the procedure, logbooks are to be review within the department (b) (4) after page completion, see **Exhibit WS-12.**

On 03 September 2020, Mr. Timothy McKendry, Associate Director QC Compliance and QC Technical Management Support provided a follow up to the three incomplete logbooks within the QC Microbiology Laboratory, see **Exhibit WS-13**. Deviation FRAD20E0749 was opened, with the root cause inadequate procedure, see **Exhibit WS-14.** The logbooks were closed, with new logbooks issued, and new process to eliminate the reoccurrence of the objectionable condition. 350 logbooks were reviewed, with incomplete logbooks isolated to the Bioburden Room. Logbook will transition to LIMS for efficiency and control purposes.

This resulted in a 483 Observation and is additionally discussed under Objectionable Conditions 2.b, Section X.

On 02 September 2020, Mr. Pete Grenier, Associate Director Facilities Operations provided an overview of the preventative maintenance program according to FBL-SOP-000081, *"Maintenance Program"*, v7, Effective date 21/07/2020. The validated application supporting PM is INFOR. For equipment that requires maintenance, an onboarding process occurs based on criticality as determined by engineering, maintenance, safety, QA and subject matter experts, with a PM plan created. A work order is created and executed electronically, with secondary review and update for the next scheduled PM event. Exceptional maintenance is conducted by work request, with emergency requests conducted within (b) (4) followed by safety, high, medium and low priority requests. I (WS) questioned if the PM for the pretreatment system is conducted in-house, with the firm indicating yes. The PM is conducted according to the manufacturer's recommendation.

Mr. (b) (6), Metrology Operations Support Group Lead provided an overview of the calibration program according to BQ-GOP-000046, *"Calibration Program"*, v4, Effective date 22/07/2020. Gauge Insight is the validated calibration database application. The owner of the

equipment with QA oversight determines assets to be calibrated, with the calibration frequency determined based on asset classification and manufacturing recommendation. Equipment that is found OOT for calibration is trended. Most assets are calibrated on-site. For asset that are no longer in use, a remove asset from service form is approved by Quality, with asset deactivated in Gauge Insight. The process of calibration includes calibration activity performed, 2nd review, with Gauge Insight update for the next calibration event. Exceptional calibrations are requested in the PM INFOR system, with calibration performed and Gauge Insight updated. There were no past due calibrations.

No objectionable observation was identified.

OOT

This section written by YXF

According to BQ-GOP-000248, *"Phenix Deviation Process"*, a deviation investigation is required for all equipment OOTs classified as GMP Critical. On Aug 26, 2020, Ms. Maggie Snow, Director Quality Compliance & Systems provided an equipment OOT list [Exhibits YXF-1] that contains 35 OOT events dated between Aug 17, 2018 to Jul 27, 2020. All deviations for the equipment OOT were classified as minor because there were no impacts on process, product strength, identity, safety, purity and quality (SISPQ). I reviewed the summaries of all OOT deviations and found that the firm's investigation and conclusion were appropriate. Note that some deviations cover multiple OOTs that occurred at same time and location. Below are two examples of OOT deviations:

FRAD20E0023**:** Data for calibration of Filter Integrity Test (FIT) units FB-3036 & FB-3037 found to be OOT, at 8 NYA. Occurrence date: Nov 14, 2020. The calibration of flow measurement for FIT units FB-3036 & FB-3037 failed (b) (4) vendor calibration. The calibration tolerance is +/- (b) % of the difference between the reference flow and measured flow. Difference percentage for FB-3036- was (b) (4) %; difference percentage for FB-3037 was (b) (4) %. There is no impact to product as a result of this event. Based on the CAPA decision (b) (4) in BQ-GOP-000249, the classification of this event was determined to be minor. FIT units FB-3036 and FB-3037 were able to be adjusted into tolerance. The calibration frequency changed to (b) (4) (b) (4) from (b) (4). No additional corrective actions are recommended.

FRAD20E0222**:** Multiple (3) Out of Tolerance (OOT) for M9 TOC/Conductivity Analyzer F-19931, F-19932 and F-19933. Occurrence date: Mar 30, 2020. This event was classified to be minor. The (b) (4) ppb verification is the same used for the system suitability for every TOC run. There is no impact to SISPQ. Impact to compliance is minor as this event represents a single control failure and did not impact the ability of process to maintain control. These instruments were able to be adjusted into tolerance. No CAPA is required per CAPA decision (b) (4) of BQ-GOP-000249. No further corrective actions are required.

No objectionable observation was identified.

Equipment Cleaning

This section written by WS

(b) (4): On 28 August 2020, Mr. Chris Blackburn, Director QA ICB (b) (4) and Mr. Foster Malcolm, Associate Director Manufacturing Engineering provided an overview of (b) (4) cleaning. I reviewed F008-ED-EPT-0068, *"Engineering Test Plan,* (b) (4) *Cycle Development of the* (b) (4) *C-3160010 and 3110020 at 8 NTA"*, v2, 12 August 2020. The (b) (4) was empty, with (b) (4) processed through the system. The process includes (b) (4), followed by WFI rinse, with rinsate and swab samples taken, acceptance criteria TOC, < (b) (4) ppb; Conductivity, ≤ (b) (4) µS/cm; Endotoxin, < (b) (4) EU/mL; Bioburden, < (b) (4) CFU/100 mL; and Swabs ≤ (b) (4) ppm. A single study was conducted with the run failing for conductivity 1,036 µS/cm, and visual inspection. A reclean was performed to specification, with cleaning verification to be performed for commercial manufacture until cleaning validation has been completed.

I reviewed F008-ED-ETP-0069, *"Engineering Test Plan:* (b) (4) *Cycle Development of the* (b) (4) *C-3110030"*, v1. Two studies were conducted to the prior acceptance criteria, with Run 1 failing for swab at the (b) (4) ppm and Run 2 swabs (b) (4) ppm (b) (4). A reclean was performed to specification, with cleaning verification performed for commercial manufacture until cleaning validation has been completed.

I reviewed the (b) (4) under F008-ED-ETP-0070, *"Engineering Test Plan* (b) (4) (b) (4) *Cycle Development of the* (b) (4) *C-3110040 at 8 NYA"*. A single run was performed with a non-conformance for a hold, automation recipe error. All testing was to specification as prior, with re-clean acceptable.

(b) (4) and Master Plan: On 31 August 2020, Mr. (b) (6), Process Engineer III, Mr. Sean O'Brien, Director Quality Contamination Control, Ms. Gretchen Brunner, Principal Quality Engineer and Mr. Dean Morris, Autonomous Production Unit Head provided an overview of the "Cleaning Master Validation Plan, *Cleaning Validation at 8 NYA Framingham Biologics Manufacturing Facility, FBL-VMP-00023"*, v4, Effective date 15/07/2020. The process includes new product introduction, change control, and assessing cleanability.

I reviewed the (b) (4) qualification under F008-ED-ETP-0067, *"Engineering Test Plan -* (b) (4) *Cycle Development of the* (b) (4) *X3200001 at 8 NYA"*. Rinsate and swab samples were taken as specified prior, with results acceptable.

I reviewed the (b) (4) -liter vessel for (b) (4) analysis under F008-ED-ETP-0073, *"Engineering Test Plan, Spray Coverage Test of the* (b) (4) *X3070001 at 8 NYA"*. The vessel internal surfaces were wetted with (b) (4), with confirmation for (b) (4). (b) (4) liters per (b) (4) of WFI was processed through the vessel for (b) (4) at a pressure of (b) (4) psig, with a single run confirming the absence of (b) (4). Post manufacture

and cleaning, the (b) (4) -liter vessel is visually confirmed through the site glass as clean, with confirmation of clean documented within the electronic batch record.

Swab Recovery: On 03 September 2020, Mr. Derek Pandolfo, Senior Manager Manufacturing provided an overview of swab recovery. I reviewed 11TRN216r1 (22 December 2011), Final Validation Report of Determination of Residual (b) (4) by TOC. The study was for (b) (4) (b) (4), with 5 materials tested: Media, (b) (4) harvest fluid, (b) (4) formulated bulk, and (b) (4) cleaning agents, with only the (b) (4) harvest fluid and (b) (4) formulated bulk applying to 8 NYA manufacture. (b) (4) to (b) (4) µg/cm^2 was applied at (different concentrations as assessed by 2 analysts in (b) (4) : (b) (4) Formulated Bulk (b) (4) µg/mL - (b) (4) µg/mL and Harvest fluid (b) (4) – (b) (4) µg/mL. Swabbing was conducted according to procedure at the time, QC-046-12, with a swab wetted with (b) (4) . The swabbing process included back and forth across the surface of the coupon, followed by up and down across the coupon, with the test swab placed into (b) (4) mL of (b) (4) . The test swabs were stored at 2 - 8°C for no more than (b) (4) , followed by sonication for (b) (4) and test. The percent recovery was (b) (4) - (b) (4) %. For the growth media, harvest fluid and formulated bulk, there was noise at the lower concentrations, with TOC values around (b) (4) - (b) (4) %. The higher concentration recovery results were acceptable and appropriate. I reviewed the current SOP for swabbing, FBL-SOP-000484, *"TOC Cleaning Verification Test for Framingham"*, with the same method of swabbing applied as in the swab recovery study. Regarding QC test sample for swabbing 19MS00889, QC-074-16, (b) (4) , I request the swab training for the individual performing sampling.

Swab training according to procedure for (b) (6) had been completed.

Furthermore, see Upstream and Downstream Equipment for cleaning.

No objectionable observation was identified.

C. ***Equipment Qualifications***

Refrigerators, Freezers and Incubators

This section written by WS

On 31 August 2020, Mr. Christopher Blackburn, Director QA ICB (b) (4) , Mr. (b) (6) , Program/Project Engineer - Commissioning, Qualification, and Validation, Mr. Michael McGrath, Senior Manager Manufacturing, and Mr. (b) (6) , Manager, Automation provided an overview of the seed incubators. I reviewed document IOV F008-ED-IOV-0017, *"Installation and Operational Verification (IOV) and Final Report for Kuhner Incubator F008-INC-102, INC-2100002"*, 04 April 2018. The IOV was standard in design. I review the empty chamber temperature distribution profile, setpoint (b) (4) °C, (b) (4) %, with an acceptance specification of (b) (4) to (b) (4) °C. (b) (4) thermocouples were positioned geometrically throughout the chamber, with an additional thermocouple external to the chamber. The study was conducted

over (b) (4) with a scan rate of (b) (4). The resulting data was acceptable for (b) (4) - (b) (4) °C temperature control. I reviewed the loaded chamber study that included the flask agitator on, with (b) flasks containing a thermocouple and (b) (4) tested for distribution profile. The study was performed over (b) (4), scan rate of (b) (4) to the prior acceptance criteria, with acceptable results.

I reviewed the second (b) (4) incubator under document F008-ED-10V-008, *"Installation and Operational Verification (10V) and Final Report for Incubator System Inc-2100003 at 8 NYA"*, Framingham Biologics. Testing was performed as described for the prior incubator, with test results acceptable.

No objectionable observation was identified.

Refrigerators, Freezers and Incubators

This section written by YXF

Cold rooms: On Aug 28, 2020, Ms. Jaclyn Blaisdell, Associate Director-Commissioning, Qualification, and Validation provided an overall of Cold room 1220 and 1131 at 8 NYV. I reviewed documents IOQR -CR-1220-8NYA-CQ-0001 and IOQR -CR-1131-8NYA-CQ-0001. These documents contain the most recent temperature mapping results of the cold rooms, dated July 22, 2020. All temperature mapping results for the empty and loaded chambers were within the specified range of 2 - 8°C. In each cold room, (b) (4) thermocouples were positioned geometrically throughout the room, with an additional thermocouple outside the cold room monitoring the ambient temperature.

(b) (4) Freezers: There are (b) (4) freezers located at 45, 74, 8 New York Ave, respectively, used for storage of cell banks. On Sep 04, 2020, Mr. (b) (6), Validation Manager provided an introduction of IOPQ of Cell Bank (b) (4). The IOPQ was standard in design. I reviewed final reports for the operational qualification of these (b) (4) freezers and temperature mapping results. (b) (4) thermocouples were positioned geometrically throughout the freezer chamber. The study was conducted over (b) (4) with a scan rate of (b) minutes. All results were well below the specified range of less than (b) (4) °C.

Freezers: On Sep 4, 2020, (b) (6) Validation Manager and Michael McGrath, Senior Manager Manufacturing, provided overview of IOPQ program for freezers and refrigerators at the manufacturing facility (8 NYA) and the QC laboratory (68 NYA). For the (b) (4) °C freezer IOPQ, (b) (4) thermocouples were positioned geometrically throughout the chamber and for refrigerator IOPQ, (b) (4) thermocouples were positioned geometrically throughout the chamber. Study were conducted over (b) (4) with a scan rate of (b) (4). All results were within the specified range. Documents reviewed included:

- F008-ED-IOQ-0008, *"Installation and Operational Qualification and Final Report for Freezer F008-*(b) (4)*-2100-024 at 8 NYA, Framingham Biologics"*

- F008-ED-IOQ-0024, *"Installation and Operational Qualification and Final Report for Sample* (b) (4) *Refrigerator F008-2100-074 at 8 NYA, Framingham Biologics"*
- F008-ED-IOQ-0009, *"Installation and Operational Qualification and Final Report for Freezer F008-*(b) (4) *-2100-025 at 8 NYA Framingham Biologics"*
- F008-ED-IOQ-0012, *"Installation and Operational Qualification and Final Report for Inoculum Prep Refrigerator F008-2100-022 at 8 NYA, Framingham Biologics"*
- IQOR-F008-2100-022-8NYA-CQ-0001, *"Standalone Report for StudyF008-ED-IOQ-0012 (Refrigerator F008-21---22) generated in response to change control 2020FRACC0034"*
- F008-ED-IOQ-0023, *"Installation and Operational Qualification and Final Report Upstream* (b) (4) *Refrigerator F008-2100-023 at 8 NYA, Framingham Biologics"*

No objectionable observation was identified.

Warehouse

This section written by YXF

I reviewed the documents for OQ, room temperature just-in-time warehouse at 8 NYA in (b) (4) and (b) (4) :

- F008-JWH-100: *"OQ Final Report for Just in Time Warehouse* (b) (4) *Study at 8 NYA Framingham Biologics"*
- F008-JWH-100-8NYA-CQ-0003: *"OQ Final Report for Just in Time Warehouse* (b) (4) *Study at 8 NYA Framingham Biologics"*

(b) (4) temperature probes and (b) (4)) humidity probes were positioned geometrically throughout the warehouse. The studies were conducted for (b) (4) . The temperature results ranged from 19.8 - 23.6°C and the humidity values were around 60% for the (b) (4) study. The temperature results ranged from 19.7 - 23.5°C and the humidity values were around 55% for the (b) (4) study. 15 - 25°C temperature control was maintained.

No objectionable observation was identified.

Upstream and Downstream Equipment

This section written by WS

On 27 August 2020, the firm provided an overview of the Master Validation Plan according to SOP FBL-VMP-000027, *"Master Validation Plan"*, Effective date 09/03/2020. The scope of the document includes Commissioning, Qualification, Requalification, Computer, and Method Validation. Furthermore, the procedure describes a traditional approach to qualification with

some leveraging applied. SOP F008-ED-ENGP-0001 V2, Effective date 25 April 2018 describes the requirements for an IOQ.

This section written by WS

Single Use Bioreactor

On 27 August 2020, Mr. Armin Opitz, Director, Manufacturing Science provided an overview of qualifications performed on the upstream equipment. I reviewed qualification F008-ED-IQ-0020, *"Installation IQ and Final Report for the Single Use Bioreactor SUB System #1 at 8 NYA, Framingham Biologics"*, Effective date March 2018. The IQ included the SUB by (b) (4), (b) (4) by (b) (4), and control system by (b) (4) with (b) (4) (distributed control system) overlay. (b) (4) housing were to be (b) (4), with housings to be washed by parts washer. An alternative was sourced, with the (b) (4) disposable. I reviewed OQ F008-ED-OQ-0013, *"Operational Qualification and Final Report for Single Use Production Bioreactor* (b) (4) *Liter #1 at 8 NYA Framingham Biologics, System F008-BRX-400"*, 11 April 2018. The OQ was standard and included training, pre-requisite list, test instrument calibration, SOPs, power-backup, filter test, OQ alarm, and control panel alarm. *Alarm testing was performed in the operational verification document F008-ED-OV-0033, "Operational Verification (OV) and Final Report for Single Use Production Bioreactor* (b) (4) *L #1 at 8 NYA, Framingham Biologics", V1.*

(b) (4): I reviewed the (b) (4) IQ under F008-ED-IQ-0024, *"Installation Qualification and Final Report for the* (b) (4) *System #1 at 8 NYA, Framingham Biologics"*. The system was constructed by (b) (4), with the system used for the PPQ studies. The IQ was standard in design with product contact surfaces (b) (4). The IQ was acceptable. I reviewed the OQ under F008-ED-OQ-0022, *"Operational Qualification and Final Report for* (b) (4) (b) (4) *System #1 at 8 NYA, Framingham Biologics"*. The OQ was standard in design, along with all other equipment operational qualifications that included training, OQ pre-request list, test equipment calibration, SOPs, automated valves, conditional approval, non-conformance log, etc. There were no deviations, with alarm testing conducted in the operational verification. Alarms were physically checked.

The facility has (b) (4), with (b) (4) located in Suite (b) under review, and the other located in Suite (b) ,which is under qualification. The (b) (4) are identical. A (b) (4) approach was taken in qualification, with 3 (b) (4) studies performed for the Suite (b) (4) and one for the Suite (b). I reviewed F008 (b) (4) -200, "(b) (4) *PQ for* (b) (4) *System 2 at 8 NYA, Framingham Biologics"*. The set point was (b) (4) for (b) (4), with (b) (4) and (b) (4) system (b) (4) used in testing. No biological were employed, with process for sanitization only. The minimum required lethality was (b) (4), based on corporate requirement. Run 1 had a mechanical failure and was disqualified, with the minimum lethality for Run 2, 3 and 4, (b) (4). I reviewed the Suite (b) (4) under "(b) (4) *PQ for* (b) (4) *System #1 at 8 NYA, Framingham Biologics"*, v1, January 2019.

The single run cycle was performed at (b) (4) for (b) (4), with a minimum lethality of (b) (4) achieved. All studies were acceptable, with the sanitized hold time set at ≤(b) (4). The requalification for the system is a paper based review.

I reviewed the cleaning validation master plan under FBL-VMP-000023, *"Cleaning Validation at the 8 NYA Framingham Biologics Manufacturing Facility"*, V4, Effective date 15/07/20. In the event a new product introduction, the cleaning process would be reassessed. (b) (4) equipment cleaning validation was conducted according to project plan, FBL-PLN-000026, *"Validation Project Plan: Cleaning Validation for Framingham Biologic Integrated Continuous Biomanufacturing"*, V1, Effective date 17/06/2019. The soilant was (b) (4), with a dirty hold time of (b) (4), with swab samples taken for TOC analysis, ≤(b) (4) ppm; and rinsate for conductivity, ≤(b) (4) µS/cm; TOC, ≤(b) (4) ppm; bioburden, ≤(b) (4) CFU/100 mL; and endotoxin, < (b) (4) EU/mL, with visual confirmation as clean.

I reviewed the cycle development report under F008-ED-EPT-0066, *"Engineering Test Plan (b) (4) Cycle Development of the (b) (4) X-2510001 and X-2560001 at 8 NYA 20 March 2019"*. One study was conducted using (b) (4), with a dirty hold time of (b) (4). The (b) (4) process included (b) (4). All results met the acceptance criteria. I reviewed the PQ under 25-0023P, *"Protocol for the PQ of the (b) (4) Process of the (b) (4) X2510001 at 8 NYA"*, 23 July 19. The single run was completed 27 July 2019, with 1 TOC failure at the pump inlet, (b) (4) ppm. A deviation investigation was conducted according to protocol, with the root cause unknown. The system was recleaned and found acceptable in preparation for manufacture. Cleaning verification will be conducted pending the completion of validation and approval, with the current clean hold pending completion of validation set at ≤(b) (4).

(b) (4): I reviewed the IQ for the (b) (4) under F008-ED-IQ-0016 1, *"Installation Qualification (IQ) and Final Report for (b) (4) System at 8 NYA, Framingham Biologics"*, 17 April 2018. The IQ was standard and included confirmation of training, IQ pre-requisites', drawings, maintenance, component loop check, system materials, pipe material, cleaning and passivation, and welding. The manufacturer of the (b) (4) is (b) (4) with the associated (b) (4) by (b) (4). The IQ was acceptable. I reviewed the OQ under F008-ED-OQ-0018 (F008-(b) (4)-300), *"Operational Qualification and Final Report (b) (4) System at 8 NYA Framingham Biologics"*, July 2018. There were no discrepancies, with alarm testing performed in the operational verification. The OQ was standard in design and acceptable.

I reviewed the (b) (4) cycle development for the (b) (4) under F008-ED-ETP-0063, *"Engineering Test Plan: (b) (4) Cycle Development of the (b) (4) X-300001 at 8 NYA, v1"*, 20 February 2019. The (b) (4) was soiled with (b) (4) with no dirty hold, cleaned immediately. The process included (b) (4) single pass with WFI rinse. Rinsate sample for conductivity, TOC endotoxin and bioburden were taken along with swabs to the prior acceptance criteria, with the first run failing and the second running acceptable. Cleaning verification for manufacture will be conducted pending validation completion.

I reviewed the (b) (4) IQ under F008-ED-IQ-007 (F008(b) (4) -301), *"Installation Qualification and Final Report for the* (b) (4) *at 8 NYA, Framingham, Biologics"*, April 9, 2018. The product dedicated system is a (b) (4), with the IQ standard in design and acceptable.

On 28 August 2020, the firm provided the qualification for the extra (b) (4) by (b) (4), an (b) (4). I reviewed IQ-F008-ED-IQ-0018, *"Installation Qualification and Final Report for* (b) (4) *at 8 NYA, Framingham Biologics, F008-*(b) (4) *-302"*, Effective date 9 April 2018. The IQ was standard and acceptable.

(b) (4): I reviewed the (b) (4) IQ under F008-ED-IQ-0019 (F008(b) (4) -401), *"Installation Qualification and Final Report for the* (b) (4) *at 8 NYA, Framingham Biologics"*, April 19, 2018. The product dedicated system is a (b) (4), with the IQ standard in design and acceptable.

I reviewed the (b) (4) under F008-ED-IQ-0026 (F008-(b) (4) -400), *"Installation Qualification and Final Report for the*(b) (4) *System at 8 NYA, Framingham Biologics"*, April 24, 2018. The IQ was standard in design and acceptable. I reviewed the OQ under F008-ED-OQ-0019 (F008(b) (4) -400), *"Operational Qualification and Final Report for* (b) (4) (b) (4) *System at 8 NYA Framingham Biologics",* 01June 2018. The OQ was standard in design and acceptable.

I reviewed the (b) (4) Cycle Development for cleaning under F008-ED-ETP-0064, *"Engineering Test Plan* (b) (4) *Cycle Development of the* (b) (4) *X3030001 at 8 NYA"*, 21 February 2019. A single study was performed with the system soiled with (b) (4), no dirty hold, cleaned immediately. The (b) (4) process included (b) (4) single pass followed by WFI rinse. Two studies were performed, with rinsate testing for TOC, conductivity, bioburden, endotoxin and swabs to prior acceptance criteria. The system was also visually inspected as clean. The test results were acceptable.

(b) (4): I reviewed the (b) (4) IQ under F008-ED-IQ-0027 (F008-(b) (4) -500), *"Installation Qualification and Final Report for the* (b) (4) *System at 8 NYA, Framingham Biologics"*, April 24, 2018. The manufacture of the system is (b) (4) (b) (4), with the IQ standard in design and acceptable. I reviewed the OQ under F008-ED-OQ-0020 (F008-(b) (4) -500), *"Operational Qualification and Final Report for the*(b) (4) (b) (4) *System at 8 NYA Framingham Biologics"*, 01June 2018. There were no discrepancies, no critical alarms and no (b) (4). The OQ was standard in design and acceptable.

I reviewed the cleaning of the (b) (4) under Engineering Test Plan (b) (4) Cycle Development of the (b) (4) X3050001 at 8 NYA, v1, 21 February 2019. The (b) (4) was soiled with (b) (4) with no hold, cleaned immediately. Three studies were performed, with rinsate testing for TOC, conductivity, bioburden, endotoxin and swabs to prior acceptance criteria. The system was also visually inspected as clean. The test results were

acceptable, with the exception of Run 2 for bioburden (b) (4) CFU/100 mL. The root cause was a sampling error.

I reviewed the (b) (4) IQ under F008-ED-IQ-0022 (F008-(b) (4) -501), *"Installation Qualification and Final Report for the* (b) (4) *at 8 NYA, Framingham Biologics"*, April 13, 2018. The product dedicated system is a (b) (4), with the IQ standard in design and acceptable.

(b) (4): I reviewed the (b) (4) IQ under F008-ED-IQ-0030 (F008-FIL-100), *"Installation Qualification and Final Report for the* (b) (4) *System at 8 NYA, Framingham Biologics"*, 29 June 2018. The manufacture of the system is (b) (4), with the IQ standard in design and acceptable. I reviewed the OQ under F008-ED-OQ-0026 (F008-FIL-100), *"Operational Qualification and Final Report for the* (b) (4) (b) (4) *System at 8 NYA Framingham Biologics"*, 30 April 2018. Critical alarm testing was conducted. The OQ was standard in design and acceptable.

I reviewed the (b) (4) cycle development for cleaning under F008-ED-ETP-0066, *"Engineering Test Plan,* (b) (4) *Cycle Development of the* (b) (4) *X3070001 at 8NYA"*, v1, 1 March 2019. The system was soiled with (b) (4), with no dirty hold, cleaned immediately. The cleaning process included WFI rinse, (b) (4) wash with (b) (4) and (b) (4) storage on the (b) (4) in (b) (4). Testing included rinsate samples for bioburden, endotoxin, TOC and conductivity, with visual inspection as clean. Run 1 failed for cycle hold and visual inspection not clean. Run 2 and 3 failed for visual inspection not clean. The root cause for cycle hold failure was the alarm parameter for weight set too tight. The root cause for visual inspection not clean was particles from the tubing suppling the cleaning solution from the (b) (4) pump. Run 4 was performed with a failure for visual inspection, particles from tubing. Run 5 included a change in tubing, with the study acceptable for rinsate samples that included visual inspection.

(b) (4) Filtration: I reviewed the (b) (4) IOQ under F008-ED-IOQ-0010 (F008-FIL-200), *"Installation and Operational Qualification and Final Report for the* (b) (4) *Filtration and* (b) (4) (b) (4) *#3090 at 8 NYA, Framingham Biologics"*. The system includes a single use (b) (4) pump. The qualification included training, IOQ pre-request, drawings, maintenance, component loop verification, system component verification, test equipment, SOPs, alarm and (b) (4) and parameter controls. Additional alarm testing was conducted under IOQ Protocol Amendment F008-ED-IOQ-0010a1, *"Installation and Operational Qualification Amendment and Final Report for* (b) (4) *Filtration and* (b) (4) *#3090 at 8 NYA, Framingham Biologics"*. Additional testing included critical quality alarms for maximum pressure and interruption alarm. Alarm confirmation was conducted via the (b) (4) system.

I reviewed the second (b) (4) filtration system for IOQ under F008-ED-IOQ-0011 (F008-ED-IOQ-0011), *"Installation and Operational Qualification and Final Report for* (b) (4) *Filtration and* (b) (4) *#3091 at 8 NYA, Framingham Biologics"*, 24 May 2018. The system and testing was the same as prior that included the IOQ protocol amendment for additional alarm

testing, F008-ED-IOQ-0011a1, *"Installation and Operational Qualification Amendment and Final Report for* (b) (4) *and* (b) (4) *#3091 at 8 NYA, Framingham Biologics"*, 16 July 2019. The testing for both systems was acceptable.

Pending the completion and approval of the cleaning validation for all systems, cleaning verification will be performed prior to manufacture.

Quality Critical Alarms: I reviewed the manufacturing system for upstream and downstream that includes quality critical alarms, alarm conditions that may have a direct impact on product quality. The (b) (4) system supports alarms monitoring that includes (b) (4), with alert and action limits. Notification of an alarm condition is on the SCADA System, with alarm banner that must be acknowledged by the operator and logged to the electronic batch record. An alarm condition includes a GEMBA, a cross functional team in the assessment of the aberrant condition that may include a deviation investigation. Alarms also include an alarm horn and visual beacon. Through (b) (4), the alarm is logged via the pi historian, then to the batch record, validated application Werum (MES, Manufacturing Execution System). The alarm is also logged into the validated application ANMS. In batch release, the alarms are review within the batch record, with alarm reconciliation to ANMS. Validation of ANMS that included loop check assures the alarms are true and accurate.

(b) (4): (b) (4) support both media and (b) (4) production where single use technology supports manufacture. I reviewed F008-ED-IQ-0032, *"Installation Qualification and Final Report for Solution Preparation* (b) (4) *at 8 NYA, Framingham Biologics, F008-*(b) (4)*-102, F008-*(b) (4)*-104, F008-*(b) (4)*-106, F008-*(b) (4)*-108, and F008-*(b) (4)*-109"*, 04 September 2018. The IQ was standard and included drawings, maintenance, loop checks, system components, instrument calibrations, materials of construction, welds, cleaning and passivation, and software testing conducted as part of (b) (4)). I reviewed the *"Operational Qualification and Final Report for Solution Preparation* (b) (4) *at 8 NYA, Framingham Biologics F008-*(b) (4)*-102, F008-*(b) (4)*-104, F008-*(b) (4)*-106, F008-*(b) (4)*-108, and F008-*(b) (4)*-109"*, 29 October 2018. OQ testing included training, OQ Pre-Request Requirements, SOPs, Test Calibrations, Critical Alarms and (b) (4), Backup Power, Automation, Setpoints, and Temperature Control Units (b) (4) control not used in manufacture. The IOQ for the (b) (4) in media and (b) (4) preparation were acceptable.

On 31 August 2020, the firm provided a continuation of (b) (4) used in manufacture. I reviewed F008-ED-IOV-0023, *"Installation and Operational Verification (IOV) and Final Report for* (b) (4)*"* redundant systems, product (b) (4). The IOV was standard in design.

I reviewed IOV Protocol F008-ED-IOV-0035, *"IOV and Final Report for the* (b) (4) *and* (b) (4) *Process* (b) (4) *at 8 NYA, Framingham Biologics"* that includes F008-(b) (4)-305, F008-(b) (4)-306 and F008-(b) (4)-402. The IOV was standard in design that included training, IV, Drawings, SOPs, Maintenance, Documents,

Component and Loop Check, Utilities, Piping Material, Piping Pressure Test, Safety, OV, Calibrations, (b) (4), Critical Parameters, Valve Automation, Setpoints and RF.

I reviewed F008-ED-IOV-0035a1, *"Installation and Operational Verification (IOV) Amendment #1 and Final Report for the Final Report for the* (b) (4) *Process* (b) (4) *at 8 NYA, Framingham Biologics F008* (b) (4) *-305, F008-*(b) (4) *-306, F008-*(b) (4) *-402"*, Effective date 19 April 2019. Testing included the (b) (4) pump loop check and alarm testing.

I reviewed F008-IOQ-0022, *"Installation and Operational Qualification (IOQ) and Final Report for* (b) (4) *at Framingham Biologics at 8 NYA, Framingham Biologics, F008* (b) (4) *-305*", 18 May 2018. The IOQ was standard and included testing for (b) (4) pressure high, weight and alarms.

I reviewed ED-IOQ-0022a1, *"Installation and Operational Qualification (IOQ) Amendment #1 and Final Report for* (b) (4) *at 8 NYA, Framingham Biologics, F008-*(b) (4) *-305"*, 15 May 2019. Critical alarms include (b) (4) contact time and (b) (4) value check. In the event of an alarm condition, visual confirmation and (b) (4) also needs to be acknowledged in resetting the alarm.

I reviewed the IOV for (b) (4) -502, F008-ED- IOV-0028, *"Installation and IOV and Final Report for* (b) (4) *502,* (b) (4) *601, and FIL-201, FIL-1-1, Product* (b) (4) *8 NYA"*. The IOV was standard in design, with (b) (4) -601 the (b) (4) . I reviewed IOV Amendment 2, *"Final Report for* (b) (4) *at 8 NYA, Framingham Biologics, F008* (b) (4) *-305, F008-*(b) (4) *306, F008-*(b) (4) *-402 and* (b) (4) *(Group 2)"*, 15 May 2019. The allowable low pH alarm was evaluated.

(b) (4) Temperature Control: On 04 September 2020, Mr. (b) (6), Program Project Lead - Commissioning, Qualification, and Validation, Mr. Derek Pandolfo, Senior Manager Manufacturing, and Ms. (b) (6), Process Senior Engineer provided an overview of qualification activities as it pertained to (b) (4) temperature control. I review F008-ED-IOV-0010, *"IOV and Final Report for* (b) (4) *Feed Temperature Control Unit System at 8 NYA, Framingham Biologics, F008-TCU-106"*, 29 March 2019. The (b) (4) vessel is (b) (4), with temperature control by TCU. Temperature control was confirmed by system RTDs at (b) (4) °C. (b) (4) °C is the commercial setpoint.

I reviewed F008-ED-IOV-0009, *"IOV and Final Report for* (b) (4) *Load Temperature Control System at 8NYA, Framingham Biologics, F008-TCV-105"*, 28 March 2018. The system is a (b) (4) that includes heating and cooling, with testing for (b) (4) °C temperature control acceptable.

I reviewed F008-TCU-102 and F008-ED-IOV-0008, (b) (4) TCU Building (b), F008-ED-IOV-0008, *"Installation and Operational Verification (IOV) and Final Report for the* (b) (4) (b) (4) *Temperature Control Unit at 8 NYA, Framingham Biologics, 8*

NYA F008-TCU-102, (b) (4) *Temperature Control Unit 21"*, March 2018. (b) (4) (b) (4) °C temperature control was verified.

Single Use System Leak Detection: On 28 August 2020, Mr. (b) (6), Process Engineer III provided an overview of the single use system leak procedure. I reviewed FBL-EWI-000039, "*SUT Response at 8 NYA"*, v1, Effective date 15/07/2020. There are five types of leaks that includes (b) (4) failure, (b) (4) failure not in-use, bioreactor failure, failure on a sample bag and tubing, and connector failure. The process for a leak includes donning PPE, GEMBA review and deviation investigation, turn off energy sources, isolate failure, spill response, and process remediation. The firm has a comprehensive leak detection program that includes work instructions for confirmation of absence of leaks during manufacture.

No objectionable observation was identified.

Laminar Flow and Safety Cabinets

This section written by WS

On 31 August 2020, Mr. (b) (6), Program Project Lead - Commissioning, Qualification, and Validation, Mr. (b) (6), Manager of Automation, and Mr. Michael McGrath, Senior Manager Manufacturing provided an overview of the LFCB used in (b) (4), with the original LFCB a (b) ft bench that has since been replaced with a (b) ft bench for more space. I reviewed F008-INC-100, *"Installation and Operational Qualification for Laminar Flow Hood at 8 NYA, Framingham Biologics"*, with the IOQ standard in design. The HEPA is tested on a (b) (4) (b) (4) basis by an outside vendor that includes system alarm testing. I reviewed the current certification that included velocity, total particle and leak test that was acceptable. The differential pressure across the HEPA as monitored by a calibrated (b) (4) is a quality critical alarm that is both a local audible and visual alarm that is tied into the validated environmental monitoring system (EMS).

No objectionable observation was identified.

(b) (4) /Clean and Sterile Hold

This section written by WS

On 01 September 2020, Ms. Jaclyn Blaisdell, Associate Director - Commissioning, Qualification and Validation, Mr. (b) (6), Process Equipment Engineer Sr., Mr. Robert Lavallee, Quality Engineer Principle provided an overview of the (b) (4) IQ. I reviewed document F008-ED-IQ-0014, *"IQ and Final Report for the* (b) (4) *System at 8 NYA, Framingham Biologics, F008-*(b) (4) *-100"*, 22 January 2018. The IQ was standard in design and acceptable. I reviewed the OQ under F008-ED-OQ-0012, *"Operational Qualification (OQ) and Final Report for the* (b) (4) *System at 8 NYA, Framingham Biologics, F008-*(b) (4) *-100"*, 14 August 2018. The OQ was standard in design and included three (3) (b) (4) studies. (b) (4)

(b) (4) were positioned geometrically throughout the chamber, setpoint (b) (4) (b) (4). The minimum lethality requirement was (b) (4), along with no (b) (4) from setpoint for the (b) (4) of timed exposure; maximum - minimum, each (b) (4) of exposure must be < (b) (4); and the (b) (4) - (b) (4) must be < (b) (4) after (b) (4) into timed exposure. Each study met the acceptance criteria without deviation. I reviewed F008-(b) (4)-100, *"Operational Qualification (OQ) Amendment 1 and Final Report for* (b) (4) *System at 8 NYA, Framingham Biologics, F008-ED-OQ-00012A1"*, v1, 09 May 2019. The OQ used the prior testing data to assess (b) (4) conditions that was acceptable.

I reviewed the PQ for the (b) (4) filter load ((b) (4)) under 25-0036, *"Performance Qualification and Final Report for* (b) (4) *System Predefined* (b) (4) *Filter Load at 8 NYA, Framingham Biologics, F008-*(b) (4)*-100"*, 05 April 2019. Preparation included (b) (4) of the filter (b) (4) valves, with the filter drug substance inlet and outlet a clean connect. The study included 1 filter and 3 runs, set point (b) (4), with the production time (b) (4) (b) (4). (b) (4) were positioned as follows: (b) (4). Additional (b) (4) were used as (b) (4) probes. The minimum lethality requirement was (b) (4) (b) (4). The biological indicators positioned next to each (b) (4) were (b) (4) (b) (4). The biological indicators are verified for population by a third party laboratory. The media used in testing for the biological indicators includes growth promotion testing. The minimum lethality was (b) (4), with the test biological indicators negative and positive controls positive.

I reviewed the bioreactor probe load under F008-(b) (4)-100 25-0037, *"Performance Qualification and Final Report for* (b) (4) *System Predefined Bioreactor Probe Load at 8 NYA, Framingham Biologics"*, v1, Effective date March 2019. The load is fixed and included the (b) (4) probe. Three runs were performed, (b) (4) cycle, with (b) (4) (b) (4), two load probes (b) (4), with the production time (b) (4) (b) (4) probes and (b) (4) probes were positioned, one positioned next to (b) (4). The minimum lethality was (b) (4), with the test biological indicators negative, positive controls positive.

An (b) (4) requalification is performed, with each load evaluated over (b) (4). A leak and (b) (4) test is performed (b) (4) prior to use.

The sterile hold time for equipment is set at ≤ (b) (4) as controlled in Athena (SAP) and documented in the batch record (MES). The two applications are link in assurance the (b) (4) sterile hold is not exceeded.

On 03 September 2020, Ms. Jaclyn Blaisdell, Associate Director - Commissioning, Qualification and Validation, Mr. (b) (6), Sr. Process Equipment Engineer, Mr. Robert Lavallee, Quality Engineer Principle, and Mr. Kyle Bigness, Sr. Manager - (b) (4)-ICBF Project provided an overview of the (b) (4) PQ. I reviewed PQ protocol 25-0040, *"Performance Qualification and Final Report for* (b) (4) *System* (b) (4) *Sterilization at 8 NYA, Framingham Biologics*

F008-AVT-100", Effective date 30 April 2019. 3 Runs were performed, with sterilization of the filter independent of the chamber. (b) (4) were positioned (b) (4) of the filter, with (b) (4) of the filter. (b) (4) biological indicator were placed at the filter on the (b) (4) side. The sterilization cycle was (b) (4), with production (b) (4). The minimum lethality requirement was (b) (4), with the minimum lethality from the three runs (b) (4). The test biological indicator were negative, with the positive control positive. The (b) (4) is changed (b) (4) and sterilized.

On 03 September 2020, Mr. Robert Lavallee, Quality Engineer Principle provided an overview of the current requalification for the (b) (4) cycle, (b) (4), and (b) (4), with an (b) (4) assessment performed (b) (4). I reviewed F008-(b) (4)-100, "*Protocol for the Requalification of the Physical Testing of the* (b) (4) *and* (b) (4) *for* (b) (4) *F008-*(b) (4)*-100 at 8 NYA Biologics 2020, RQ-F008-*(b) (4) *100-8NYA-CQ-0001"*, May 2020. A single study was performed for each cycle, with the (b) (4) for the (b) (4) cycle including (b) (4) positioned geometrically, exposure time (b) (4) at (b) (4). The minimum lethality was ≥ (b) (4) and acceptable. I reviewed the (b) (4) requalification that included (b) (4) and (b) (4) biological indicators, positioning the same as PQ. The minimum lethality was (b) (4), with biological indicator data acceptable.

No objectionable observation was identified.

Requalification

This section written by WS

On 03 September 2020, Mr. (b) (6), Validation Manager and Mr. (b) (6), Program Project Lead - Commissioning, Qualification, and Validation provided an overview of requalification according to VMP Requalification, *"Framingham FQ-VMP-000006-10.0"*, 25/06/20. Equipment for requalification is broken into three categories: Category 1 requires a quality system review (QSR) and physical test, with (b) (4) loads tested (b) (4), (b) (4) and (b) (4); Category 2 requires a QSR that includes CTUs, (b) (4) physical mapping; and Category 3 includes no timed based requalification. The QSR review includes deviations, CAPAs, and SOPs, with the firm currently current on requalifications.

No objectionable observation was identified.

Material Management

Storage/Distribution, Quarantine and Flow

This section was written by YXF

All raw materials are ordered, received, sampled, tested, and released at the (b) (4) (b) (4) facility, which is outside of this inspection. A dedicated (b) (4) belonging to the firm transports the materials from the (b) (4) facility to the warehouse at 8 NYA. FBL-SOP-000661 governs the process for transporting, receipt, and storage of controlled materials and indirect packages inside and outside of controlled areas at Framingham Biologics and Biosurgery.

Upon receipt, the materials are inspected according to delivery order for potential damage. Materials stored in the GMP warehouse are electronically managed with Athena, a validated module within SAP. The GMP warehouse includes (b) (4) temperature probes for continuous monitoring and (b) RH probes.

We (WS and YXF) toured the warehouse on Aug 26, 2020 and found the materials were well organized and segregated.

There are (b) (4) 2-10°C cold rooms within the warehouse which are for storage of raw materials, intermediates, and manufactured DS. At the time of our tour, there was no DS or raw materials within the cold rooms. Some standards for UPLC assay were stored in the cold room.

No objectionable observation was identified.

Production System

A. Processes

Process Validation Program

This section written by WS

On 28 August 2020, Mr. Armin Opitz, Director of Manufacturing Science and Ms. Gretchen Brunner, Principle Quality Engineer provided an overview of drug substance PPQ studies from a microbiological control perspective. I review FBL-RPT-000510, *"Process PQ Final Report for the* (b) (4) *Integrated Continuous Biomanufacturing* (b) (4) *Process"*, v1.0, Effective date 04/03/2020. Microbiological testing for bioburden and endotoxin is performed at the (b) (4) of (b) (4), load for the (b) (4), with the bioburden acceptance criteria < (b) CFU/10 mL and endotoxin ≤ (b) (4) EU/mL. Test results were < (b) (4) EU/mL and (b) CFU/10 mL. The product is further processed through the (b) (4) into a (b) (4) liter (b) (4) followed by (b) (4) micron filtration into a (b) (4) liter SUT. (b) (4) SUTs are (b) (4) for forward processing. As a process improvement, bioburden was taken (b) (4) micron filtration, with (b) (4) to be ≤ (b) (4) EU/mL and (b) CFU/10mL, results < (b) (4) EU/mL and (b) CFU/10mL.

I reviewed FBL-RPT-000511, *"Process Performance Qualification Final Report for the* (b) (4) *Integrated Continuous Biomanufacturing* (b) (4)

(b) (4) *Process"*. Endotoxin was taken at the (b) (4) of the (b) (4) hold for the 3 batches, acceptance criteria < (b) (4) EU/mL, results < (b) (4) EU/mL, with no (b) (4) micron filtration. Testing was acceptable.

I reviewed the (b) (4), acceptance criteria ≤ (b) (4) EU/mL and bioburden inadvertently not documented, results < (b) (4) EU/ml and bioburden (b) CFU/10 mL.

I reviewed the (b) (4) load FBL-RPT-000512, *"Process PQ Final Report for the* (b) (4) *Integrated Continuous Biomanufacturing* (b) (4) *liter* (b) (4) *"*, with the acceptance criteria for endotoxin < (b) (4) EU/mL and bioburden ≤ (b) (4) CFU/10 mL, results < (b) (4) EU/mL and (b) CFU/10 mL, respectively.

I reviewed the (b) (4) for the (b) (4) liter (b) (4), with an endotoxin and bioburden specification of < (b) (4) EU/mL and (b) CFU/10 mL, respectively. Test results were < (b) (4) and (b) (4) EU/mL and (b) CFU/10 mL.

I reviewed the (b) (4) under FBL-RPT-000513, *"Process Performance Qualification Final Report for the* (b) (4) *Integrated Continuous Biomanufacturing* (b) (4). The endotoxin and bioburden acceptance specification were ≤ (b) (4) EU/mL and < (b) (4) CFU/10 mL, respectively. Results were less than < (b) (4) EU/ml and (b) CFU/10 mL. I reviewed the data for the second concentration, with the endotoxin specification ≤ (b) (4) EU/mL and ≤ (b) (4) CFU/10 ml, results < (b) (4) EU/mL and (b) CFU/10 mL, respectively.

I reviewed the (b) (4) FBL-RPT-000541, *"Process Performance Qualification Final Report for the* (b) (4) *Integrated Continuous Biomanufacturing* (b) (4) *-ICB) Formulation and* (b) (4) *Filtration"*, v1.0, Effective date 04/03/2020. The load bioburden and endotoxin acceptance criteria is ≤ (b) (4) CFU/10 mL and ≤ (b) (4) EU/mL, with test results (b) CFU/10 mL and < (b) (4) EU/mL, respectively.

I reviewed the test data from the drug substance, with specifications of ≤ (b) (4) CFU/100 mL and < (b) EU/mL, results (b) CFU/100 mL and < (b) (4) EU/ml, respectively.

Bioburden and endotoxin IPC testing was always (b) (4) to (b) (4) micron filtration.

On 31 August 2020, Mr. Armin Opitz, Director Manufacturing Science provided an update to (b) (4) clearance according to FBL-RPT-000515, *"Final Report for the* (b) (4) *-Integrated Continuous Manufacturing Biomanufacturing* (b) (4) *at Scale Impurity Characterization Samples"*. Once the product is processed through the (b) (4) stage, the (b) (4) is only present at residual levels.

(b) (4) Storage Solutions: On 31 August 2020, Mr. (b) (6), Process Engineer III, Mr. Sean O'Brien, Director Quality Contamination Control, Ms. Gretchen Brunner, Principle Quality Engineer, and Mr. Dean Morris, Autonomous Production Unit Head provide an overview of the

(b) (4) attached after the (b) (4) system. The process includes removing the manufactures storage solution that aids in sterilization that includes a flush with (b) (4). The continuous manufacturing process over (b) (4) is a (b) (4) system, no bioburden or endotoxin is taken until (b) (4) of (b) (4), at the (b) (4) liter (b) (4). Product is (b) (4) after (b) (4) from a (b) (4), followed by (b) (4).

The (b) (4) by (b) (4) is stored in (b) (4) at ambient. (b) (4) PM of the (b) (4) is to remove the (b) (4), with inspection of the (b) (4) and cleaning. Endotoxin and bioburden is a not sampled, with the storage solution anti-microbial. The process of storage solution exchange includes (b) (4). I reviewed FBL-RPT-000758, *"Process Validation Final Report for (b) (4) Integrated Continuous Manufacturing (b) (4) Life Time"*, v1.0, Effective date 13/07/2020. The acceptable bioburden and endotoxin testing taken post (b) (4) (b) (4) was ≤(b) (4) CFU/10 mL and ≤(b) (4) EU/mL.

I reviewed the (b) (4), with storage in (b) (4). The (b) (4) is stored at ambient, with manufacturing conducted at (b) (4) °C. (b) (4) preventative maintenance is the same as prior. The process of storage solution exchange includes (b) (4). Bioburden and endotoxin is taken post (b) (4) (b) (4). I reviewed FBL-RPT-000759, *"Process Validation Final Report for (b) (4) Continuous Manufacturing (b) (4) Lifetime"*. The resulting data for bioburden and endotoxin was ≤(b) (4) CFU/10 mL and ≤(b) (4) EU/mL, with results <(b) CFU/10 mL and <(b) (4) EU/mL, respectively.

A mock (b) (4) LAL life time, blank run is performed (b) (4) cycles and for the (b) (4) cycle for protein carry over and endotoxin for the (b) (4). All data to date was acceptable.

I reviewed the (b) (4) stored in (b) (4), with (b) (4) PM as prior. The (b) (4) exchange includes (b) (4) followed by bioburden and endotoxin testing. I reviewed FBL-RPT-000761, *"Process Validation Final Report for (b) (4) Integrated Continuous Manufacturing (b) (4) Lifetime"*, v1.0, Effective date 02/07/2020. Mock life time testing is conducted (b) (4) for endotoxin, acceptance limit ≤(b) (4) EU/mL, with results < (b) (4) EU/mL. The (b) (4) specification for bioburden and endotoxin is ≤(b) (4) CFU/100 mL and ≤(b) (4) EU/ml, respectively, with test results <(b) CFU/100 mL and <(b) (4) EU/mL.

On 01 September 2020, Mr. Armin Opitz, Director Manufacturing Science, Ms. Julie Barker, Director of Quality Assurance, and Mr. Franqui Jimenez, Head, Next Generation Process

Development provided an overview process validation under DQ-GOP-000281, *"Process Validation for Biologics"*, v1, Effective date 05/06/2019. The scope of the procedure is all U.S. sites, with the procedure a corporate directive. I reviewed FBL-VMP-000024, *"SUB VMP Process Validation at Framingham Biologics, MA, 8 NYA"*, v4, Effective date 24/08/2020. Process validation is based on FDA guidance and includes development, PPQ and process monitoring and continuous improvement

A review of the PPQ runs from a microbiological perspective was acceptable.

Reference Discussion Item WS-1 in Section XII, GENERAL DISCUSSION WITH MANAGEMENT.

Formulation

This section written by YXF

(b) (4) [redacted]

On Aug 27, 2020, together with (b) (6) [redacted], Sr. Manager-Manufacturing, (b) (6) [redacted], Sr. Manufacturing Engineer, and Michael McGrath, Sr Manager-Manufacturing, I reviewed the electronic batch record for the (b) (4) [redacted] step of PPQ batches.

No objectionable observation was identified.

(b) (4) [redacted] Validation

This section written by YXF

On Aug 28, 2020, Mr. (b) (6) [redacted], Project Lead provided an overview of (b) (4) [redacted] homogeneity qualification studies for solutions. The solution (b) (4) [redacted] studies are governed by Document 25-0010P entitled *"Performance Qualification (PQ) Protocol for* (b) (4) [redacted] *Homogeneity of the* (b) (4) [redacted] *at 8 NYA"*. Solution (b) (4) [redacted], and hold time was validated following a risk-based approach (b) (4) [redacted] and worst case). (b) (4) [redacted] of each solution was demonstrated to effectively produce the defined solution specifications prior to use. Minimum (b) (4) [redacted] times were also defined for all intermediates to ensure homogeneity relative to the measured parameters. I reviewed the final report for the (b) (4) [redacted] homogeneity studies (Document #25-0010FR). Solutions studied include (b) (4) [redacted]

(b) (4) I also reviewed the actual study record for (b) (4) study of (b) (4). This solution was chosen for further review because it has the highest viscosity and represents the worst case for (b) (4). The results indicate that (b) (4) was sufficient to generate solution with acceptable homogeneity.

On Aug 31, Mr. Armin Opitz, Director-Manufacturing Science provided an overview of (b) (4) hold study. I reviewed the (b) (4) stability report for 8 NYA. For (b) (4), the testing methods used in the (b) (4) stability study include pH, Conductivity, and RI. I expressed my concerns on potential oxidation of (b) (4) that may not be detected using testing methods in the study. Armin Opitz stated that (b) (4) raw material ordered from the (b) (4) facility were unopened intact bottle in their original package and storage of (b) (4) solution for a maximum of (b) (4) should not generate a significant amount of oxidation.

No objectionable observation was identified.

Batch Record

This section written by YXF

The firm provided executed batch records for each unit operation of the PPQ runs, including (b) (4) (b) (4), the ICB segment and one of the three downstream runs for manufacture of DS batch (b) (4). However, the batch records provided in the submission were not readable because of their length and unclear organization. For example, executed batch record (b) (4) for just the bioreactor unit operation for one batch contains 9998 pages. During the inspection, I had multiple discussions with the firm on the batch record. On Aug 27, (b) (6), Sr. Manager-Manufacturing, (b) (6), Sr. Manufacturing Engineer, and Michael McGrath, Sr. Manager-Manufacturing provided an overview of the design approach for the electronic batch record (eBR) in the Manufacturing Execution System (MES) **[Exhibit YXF-2; Exhibit YXF-3]**.

The Firm acknowledged that the electronic batch record did not translate well in the PDF included in the submission. In addition, the PDF batch records did not include key information that determines the performance of the manufacturing process and control, such as Key Process Parameters (KPP), Critical Process Parameters (CPP), In-process Control (IPC) values, and performance trends (e.g. chromatographs). The firm explained that data collection and recording has been decentralized and the information on process parameters and in-process controls are historized in some GxP systems other than MES including:

- Statistica: A system that pulls data in from multiple systems for process analysis
- Spotfire: A program that displays and trends data
- Manufacturing Execution System (MES): A system comprised of electronic batch records and logs
- Laboratory Information Management System (iLIMS): A laboratory management system that contains off-line quality control results

- (b) (4): Automation system that manages and monitors the production process real time
- Pi Historian: A systems that historizes data from (b) (4)

The Firm stated that PDF version of eBR is not used in the daily operation, but only for regulatory submission. I reviewed the eBRs for the ICB segment (production bioreactor and (b) (4) steps) and (b) (4) steps in the MES. The MES contains active links to other associated systems, such as (b) (4) and Electronic Work Instructions (EWIs) and data collected. The eBR has sufficient elements to ensure the execution of the manufacturing process. I requested the operation parameters that were monitored during the product bioreactor run in PPQ campaign, including (b) (4) (b) (4) **[Exhibit YXF-4]**, as well as the representative (b) (4) (b) (4) at different harvest time **[Exhibit YXF-5]**. All data reviewed indicates the PPQ run was under a well-controlled status.

On Sep 03, 2020, I had another discussion with Tara Girshick, Associate Director-Quality, (b) (6), Sr. Manager-Manufacturing, Carolyn Trott, Head of Quality. I expressed that submitting very large size batch records that are not readable and do not contain essential information on process control is not acceptable. The Firm acknowledged the problem but stated that the current PDF version batch record was generated by the eBR application and there is no way to generate a new version in a short period of time. The Firm committed to working with the eBR provider WERUM to generate a readable informative PDF version of the batched record and to submit it to the upcoming (b) (4) Report. In addition, to address an IR dated Aug 28, 2020, the firm provided a guide to the Agency that facilitate our review of the current batch record and supplemental information that includes as Key Process Parameters (KPP), Critical Process Parameters (CPP), In-process Control (IPC) values, and performance trends (e.g. chromatographs).

Note: I have reviewed supplemental information provided in an attachment in SN 0430 and determined that the firm addressed questions for the batched record, acceptable.

No objectionable observation was identified.

Support Areas (Media and (b) (4))

This section written by WS

On 27 August 2020, Ms. (b) (4), Principle Quality Engineer, Quality Assurance Contamination Control, Mr. Armin Opitz, Director, Manufacturing Science, Mr. Sean O'Brien, Director, Quality Contamination Control, and Mr. Kyle Bigness, Sr. Manager -(b) (4)-ICBF Project provided an overview of microbiological control according to SOP-FBL-LRA-000027, *"HACCP for Evaluation of Microbiological Control for the Second Generation* (b) (4) *Process"*. All (b) (4) are (b) (4) micron filtered into a sterile (b) (4) single use bag, with sampling for

endotoxin at point of (b) (4) filtration, with bioburden at point of use, end of hold. The hold times have been validated.

Regarding (b) (4) micron filtration in the downstream process, all (b) micron filters are integrity tested where an (b) (4) step occurs, along with the (b) (4) step. The only completed batches produced to date are the 3 PPQ runs, with no bioburden or endotoxin alert or action level excursions from either upstream of downstream manufacture.

On the 31 August 2020, Mr. Armin Opitz, provided an overview of the media and (b) (4) hold times, with media holds supporting (b) (4), worst-case. (b) (4) was considered worst-case based on the ambient storage condition. *I reviewed FBL-RPT-00105, "Interim Report for the Performance Qualification of Microbiological Hold Time for Process Intermediates and Prepared Solutions at 8 NYA"*, v1, Effective date 27/08/20. The study included testing out to (b) (4), still in-progress, with results for microbiological and endotoxin testing for different storage systems acceptable. Endotoxin is taken post formulation, with bioburden at time of use.

No objectionable observation was identified.

Lots Made and Reprocessing

This section written by YXF

On Sep 01, 2020, Ms. Alisa Routhier, Associate Quality Director and Ms. (b) (6), Process Engineer III provided an overview of manufacturing history of the Commercial manufacturing facility at 8 NYA [Exhibit YXF-6]. Batches made in this facility include (b Shakedown runs, (Engineering runs, and 3 PPQ runs. Two seeds (b) (4) runs (b) (4) and (b) (4) were terminated as planned. There was an ongoing batch at the SUB/(b) (4) step.

There were no lots that were reprocessed. No reprocess is allowed in the (b) (4) -IBC process.

No objectionable observation was identified.

Cell Bank and Inoculation

This section written by YXF

I reviewed the master plan FBL-REF-000118 that provides an overview of the testing, storage, inventory, disaster recovery, and performance monitoring strategy for cell banks in the firm. There were (b) (4) tanks for cell bank storage located at 45, 74, NYA, respectively. On Aug 28, 2020, I toured the cell bank storage facility at Building 45, with Mr. (b) (6), Manufacturing Site Manager, Ms. Emily Fullerton, Associate MSAT Director, and Ms. (b) (6), Manufacturing Supervisor. The temperature readings of the (b) (4) dewar were (b) (4) °C (Probe (b) at (b) (4)) and (b) (4) (Probe (b) on the (b) (4)). Mr. Jon Lowe explained the control of access to the cell banks. Less than (b) (4) people have the access to the cell bank facility.

The (b) (4) dewar is secured by lock and the key, with access controlled by the Quality team. There were clear labels in the (b) (4) dewar indicating the calibration and service status. Cell bank access is recorded in a paper based log book. I reviewed the Working Cell Bank log books of both 45 and 74 NYA, and found that the number of vials removed, number of vials remaining, and the intended uses of the vials were clearly recorded.

There is another (b) (4) dewar at 8 NYA for short term storage of WCB vials that will be used for the upcoming manufacture. The same as the (b) (4) dewar in Build 45, this (b) (4) dewar is access restricted and secured by lock and the key, maintained by quality. The (b) (4) dewar is monitored and alarmed by EMS. Cell banks for (b) (4) ICB and (b) (4) ICB are store in this (b) (4) dewar and they are segregated by separate racks. No more than (b vial for each cell bank are stored in this (b) (4). There is a (b) (4) dewar with temperature monitoring for transport cell bank vials to the inoculation seed room. FBL-SOP-000079 describes detailed procedure for (b) (4) storage, replacement, handling, and inventory of cell banks within the GMP areas. I reviewed this SOP and found it contains sufficient detailed instruction to ensure proper handling of the cell banks and (b) (4) storage dewar.

All (b) (4) dewars were adequately qualified (see freezer section).

To start a DS manufacturing process, a vial of WCB (Lot (b) (4)) was used to inoculate a (b) (4) mL (b) (4) flask, then the cells were (b) (4) in (b) (4) flasks sequentially. The (b) (4) flask steps were performed in Grade A Laminar Flow Hood in a Grade C Suite. Cells from the (b) (4) mL (b) (4) flask are then transferred into a (b) (4) L cell bag, followed by (b) (4) cell bags. These (b) (4) bag steps are performed in a Grade D environment for the upstream process. During the inspection, there were no activities in the flask, inoculation seed room.

No objectionable observation was identified.

Cell Culture and Harvesting

This section written by YXF

Production cell culture is performed within a (b) (4) L signal-use bioreactor (SUB) and is run in (b) (4) mode, with cells retained in the reactor by (b) (4) filters. In the first (b) (4) of operation, cells grow to achieve the desired cell density. Beginning on approximately (b) (4), the harvest from the (b) (4) is continuously captured by the integrated (b) (4) that uses (b) (4). The total culture duration is approximately (b) (4).

During our tour to the manufacturing facility on the first day of the inspection (Aug 26, 2020), the production bioreactor was on the (b) (4) of operation. The bioreactor, (b) (4) solution, and the fresh medium were all on scales to monitor weight. The medium in (b) (4) L signal use (SUT) bags, (b) (4) solution for (b) (4), bleed waste, and growth phase waste

are located within the Logistics Corridor, which is a controlled not classified (CNC) space. These solutions are aseptically connected to the bioreactor via single use (b) (4) tubing.

I observed that there are two differences between the actual process and the description in the (b) (4):

1. In the actual process, there are (b) (4) units running in (b) (4), but only one in the submission.
2. The harvest from (b) (4) passes through a (b) (4) L harvest vessel bags to the continuous capture (b) (4). The harvest bag is also connected to (b) (4) L overflow bag to which extra harvest is collected. The material in the overflow bag is discarded. However, the harvest bag and the overflow bag were not included in the process description in the (b) (4).

*I discussed these discrepancies with the upstream manufacturing team and was provided with (b) (4) ICB process diagram **[Exhibit YXF-7]**. We issued an IR to request the applicant to update (b) (4) to reflect all equipment used, including number of (b) (4) units and intermediate holding vessels.*

During our tour to the facility, the (b) (4) was not running per normal operation. I was told that the (b) (4) was not ready to run. The harvest bag was full, and the harvest was flowing to the overflow bag. I had a discussion with Mr. Michael McGrath, Sr. Manufacturing Manager. He explained that the pump pressure was found to be higher than the normal operation range during (b) (4) preparation. The root cause was that one (b) (4) valve was connected in an opposite orientation. The (b) (4) setup was discard and a new (b) (4) setup installed, sanitized, and (b) (4).

I checked the status of the (b) (4) with Mr. Michael McGrath on Sep 4, 2020 and was informed that the (b) (4) has been running normally.

No objectionable observation was identified.

Purification and Formulation and Bulk

This section written by YXF

The (b) (4) are further processed by the downstream operation steps, including (b) (4) and filtration and fill. None of these operation units was in operation during our inspection. All equipment including (b) (4) and vessels for intermediates were maintained well.

No objectionable observation was identified.

(b) (4) Life Time Studies and Long-Term Storage

This section written by YXF

On Sep 3, 2020, Mr. Armin Opitz provided an overview of (b) (4) use studies. BQ-GOP-000280 governs the lifetime validation of (b) (4) and (b) (4). The life time validation for (b) (4) at each (b) (4) step is performed according a specific protocol. I reviewed the report for (b) (4) Lifetime, which was conducted under protocol FBL-PTM-000057 "(b) (4) Lifetime Validation Protocol for the Second Generation (b) (4) (b) (4)". The results in the report showed that (b) (4) lifetime validation successfully completed (b) (4) cycles on the (b) (4) for the production of (b) (4) ICB at the 8 New York Avenue Manufacturing Facility in Framingham, MA. All acceptance criteria were met during the execution of this validation. The (b) (4) lifetime will continue, and this report will be updated on an (b) (4) basis to document the cycles performed in the previous (b) (4).

No objectionable observation was identified.

Fill and Dispensing

This section written by WS

On 02 September 2020, we (WS and YXF) observed the simulated drug substance fill process. The drug substance post (b) (4) filtration is sampled for bioburden and endotoxin from the (b) (4) liter bulk (b) (4), with an approximate volume during manufacture of (b) (4) liters. Post (b) (4) -liter (b) (4), the drug substance transfer line is attached to the (b) (4) pump by clean connect through a (b) (4) micron filter to a manifold containing all clean connects. A pressure switch upstream of the (b) (4) micro filter is set a (b) (4) psi (not calibrated), with the post integrity tested (b) (4) micron filter having an (b) (4) psi maximum limit. Components supporting manufacture that includes the fill manifold are scanned into the electronic batch record for traceability. (b) (4) operator performs the setup, with a (b) (4) operator confirming the setup. The drug substance is filled into (b) (4) liter (b) (4) bags within a (b) (4) by clean connect, designed as a complete unit with lid, with the process controlled by SCADA and documented by associated electronic batch record. I (WS) observed at the SCADA the tare of the drug substance (b) (4) bag (b) (4) for filling, with fill to (b) (4). During the filling process, the absence of leaks was visually confirmed and documented. The area includes a visual and audible indicator for differential pressure. At the end of the fill process, the fill line was drained to bag, with the fill line (b) (4) (validated), inspected and (b) (4), with 2 labels printed. One label was applied to the bag, with the other to the outside of the (b) (4). Label information included Batch #, Part #, Description, Weight, Expiration, and Barcode. The drug substance is sampled from the (b) (4) at the fill finish facility. The number of bag filled per batch is (b) - (b), and upon completion of the fill for all bags, the (b) (4) containing drug substance are stored at 2 - 8°C.

No objectionable observation was identified.

Gown Qualification

This section written by YXF

I reviewed FBL-EWI-000002 *"Electronic Working Instruction (EWI) on Gowning"* effective 07/17/2020. The purpose of this procedure is to provide instruction for personnel gowning in controlled and classified areas of the manufacturing facility at 8 NYA. The procedure includes general guidelines, items used for gowning, and gowning requirements for classified and CNC areas.

On Aug 28, Mr. (b) (6), Sr Manufacturing Manager and Mr. (b) (6), Principle Quality Engineer provided an overview of the gowning procedure and staff training. Gowning training includes courses (Basic Gowning Requirement for Manufacturing Controlled Areas and General Principle of Growing), Structured Discussion on the EWI (FBL-OJT-000567), and On Job Training (OJT). I requested and reviewed the training records for three of the most recent hired employees. The employees completed training before entering the manufacturing areas.

During the inspection walk-through of the facility on Aug 26, 2020, we (WS and YXF) went through gown OJT and gowned according to Sanofi staff direction into the manufacturing facility.

In the response to the Covid-19 pandemic, the firm implemented (b) (4) and mask requirements for CNC areas at the Framingham Campus **[Exhibit YXF-8]**. This action contained clear instruction for mask requirements within the non-controlled areas, social distancing, and mask change and requirements to enter the manufacturing areas.

No objectionable observation was identified.

Container Closure Integrity

This section written by YXF

(b) (4) bags (b) (4) are used for DS storage and shipment. During the mock fill operation on Sep 03, 2020, I observed that the operators carefully opened the package of the bag and tubing and checked their integrity. The bag was placed within the (b) (4) drum as the secondary container. There was no leakage found during the fill operation. The mock fill was successfully completed. There were no changes made to the container closure system.

No objectionable observation was identified

DS Shipping Validation

This section written by YXF

On Aug 28, 2020, Mr. (b) (6), Site Supply Chain Supervisor provided an overview of the DS shipping validation. I reviewed NBO-SOP-000343, *"Shipping of* (b) (4) *Formulated Bulk in* (b) (4) *Active Shipper"* for the preparation and shipping of DS to the DP manufacturing site.

The primary container is a (b) (4) L (b) (4) bag, which is secured within a (b) (4) drum (secondary container) and placed in a (b) (4) thermal pallet shipper for transportation between the formulation and the fill/finish manufacturing facilities. No changes were made to the DS shipping system and no shipping validation was performed for 8 NYU. I interviewed Mr. Dean Morris, Autonomous Production Unit Head and (b) (6), Material Supervisor about the preparation process at 8 NYA. I requested and reviewed the temperature monitoring data for 3 PPQ batches (b) (4), (b) (4), and (b) (4) during shipment. The transport system maintained product temperature within the specified temperature range of 2 to 10 °C during the entire shipping process.

No objectionable observation was identified.

B. Contamination/Mix-up

Personnel/Material Segregation and Waste Control

This section written by YXF

On Sep 03, 2020, Mr. Dean Morris, Autonomous Production Unit Head and Mr. Kyle Bigness, Sr. (b) (4) ICB Project Manager provided contamination control and waste flow in the production areas as shown in the (b) (4) ICB process diagram **[Exhibit YXF-7].** The established gowning procedures specified the gowning requirement at various classified and controlled areas and prevents personal contamination. Raw materials transition through an (b) (4) with cart to cart transfer. All items are sanitized with (b) (4) with a contact time more than (b) (4). The firm leverages single use systems and employs a (b) (4) manufacturing process to reduce risk of contamination. The media and (b) (4) from the CNC Logistics Corridor are directly aseptically connected to the manufacturing process ballrooms via single use tubing; and waste solutions from the manufacturing process are directly piped (b) (4) to the waste container at CNC corridor **[Exhibit YXF-7].** During the tour to the facility, we observed that every item brought into the production areas was adequately cleaned and sanitized.

The firm also performed a risk evaluation of potential contamination of SARS-CoV2 and control measures **[Exhibit YXF-8].**

No objectionable observation was identified.

Multi-product Manufacturing and Area Changeover

This section written by YXF

On Aug 28, 2020, Chris Blackburn, QA Director-(b) (4) provided an overview of multiproduct controls [**Exhibit YXF-10**]. Document F008-ED-GNRL-0386 describes multiproduct manufacturing at ICBF at 8 NYA [Exhibit YXF-11]. (b) (4) ICB is the first process introduced to 8 NYA in Suite (b) (4) . The second process pending introduction is the (b) (4) Integrated Continuously Bioprocessing ((b) (4) -ICB) in Suite (b) (4) . The firm assessed risks associated with implementing (b) (4) ICB as part of the CCR 2019FRACC0056: i) product cross contamination, ii) microbial/vial contamination, iii) product component/material segregation, iv) equipment configuration, v) use of appropriate product-specific procedures and vi) shared utilities. Currently, the only area where (b) (4) ICB and (b) (4) ICB overlap is the inoculum room. The risk of cross-contamination during changeover is low. The firm states that additional tech transfers are planned for 8 NYA and require CCRs and regulatory notifications.

No objectionable observation was identified.

Laboratories (Chemistry)

This section was written by YXF

On Sep 01, 2020, Mr. Mark Roy, QC Director, provided an overview of the QC system, including instrument qualification, calibration and maintenance, method development, validation, analyst training, sample management, and laboratory investigations. I (YXF) toured to the Chemistry QC Laboratory at 68 NYA with a QC team, including Mr. Mark Roy, QC Director, Mr. (b) (6) , QC Principle Scientist, Ms. Kelly DeSousa, QC Manager, Ms. Nancy Watkins, QC Manager, and (b) (6) , Principle Analyst.

No objectionable observation was identified.

Instrument Qualification, Calibration, Maintenance and Methods

This section written by YXF

Qualification of Laboratory instrument is governed by QFBL-VMP-000012, *"Sub or Site-VMP: Laboratory Equipment Qualification (LEQ), Framingham Biologics"* and FBL-SOP-000994 *"Requalification Operations and Life Cycle"*. During the QC laboratory tour, I (YXF) checked the qualification records of SoloVPE UV-VIS Spectrophotometer for $A_{280\ nm}$ protein concentration test, UPLC systems for RP-UPLC and SEC-HPLC purity tests. For the SoloVPE system, the internal preventive maintenance is performed (b) (4) and the vendor maintenance and calibration is performed (b) (4) . All maintenance and calibration activities were noted in the instrument Log Book. For the HPLC/UPLC systems, the firm performs internal maintenance (b) (4) , the activities include cleaning, checking valves, pump pressure, lamp time

and intensity, and flow rate. Vendor maintenance is performed (b) (4). Labels applied to instruments indicate that maintenance and calibration activities were performed as scheduled. I also randomly checked the pipettes, solutions in the laboratory and no events of expiration were identified.

I reviewed the SOP for enzyme activity assay and RP-UPLC assay. There were no testing activities for (b) (4) during the inspection. During the QC laboratory tour, I (YXF) observed a mock performance of the enzyme activity assay and RP-UPLC assay. The mock enzyme activity assay was performed by (b) (6) according FBL-MTD-000069. He displayed deep understanding of the assay and good skills of sample handling, pipetting, and instrument operation. The mock RP-UPLC assay was performed by (b) (6) according FBL-MTD-000068. She performed sample loading and assay setup, but the UPLC running was not performed. Instead, she used a chromatogram to show the data analysis. The SOP contained clear instruction for integration and detailed examples for peak integration as it pertains to the intermediate, DS, and DP.

I reviewed the SOP FAD13-040 for SE-HPLC for Determination of Aggregates. A sensitivity control sample is used in the system suitability testing. On Sep 1, 2020, I (YXF) interviewed Mr. Mark Roy, QC Director, Mr. (b) (6), QC Principle Scientist, and Mr. (b) (6), Principle QC analyst. The sensitivity control sample was prepared from heat-treated (b) (4) DS and was qualified. I reviewed the requalification results [**Exhibit YXF-12**]. No significant changes were observed when stored at < (b) (4) °C for up to (b) (4) days. The most recent re-test was performed on May 11, 2020.

The firm has a Global Operating Procedure (BQ-GOP-000018) that provides an approach to maintain and ensure control over a test method's suitability and compliance status throughout its use.

No objectionable observation was identified.

C of As for Intermediate and Reference Standards, Trending

This section written by YXF

On Aug 31, 2020, Mr. Timothy McKendry, Associate QC Director, provided an overview of the Reference Standard program, which is governed by BQ-GOP-000259, *"Biological Primary and Working Standard Program"*, Version 2.0, effective Oct 31, 2018. The generation, qualification, performance monitoring, and requalification for (b) (4) ICB reference are governed by FBL-SOP - 001260, *"*(b) (4) *-ICB Analytica Reference Standards"*.

Currently, one primary standard lot (b) (4) and one working standard (b) (4) were prepared from ICB material and qualified. I reviewed the qualification reports for these reference standards and found they are suitable for their intended uses. These standards have not implemented. I confirmed with the firm that they will summit the qualification data to the Agency for approval

prior to implementation. An IR was issued that clarified the requirement for reference standard details.

No objectionable observation was identified.

OOS Procedure and Investigations

This section was written by YXF

On Sep 2, 2020, Mr. Timothy McKendry, Associate QC Director provided an overview of the OOS procedure. The Laboratory Events (LEs) investigation is governed by BQ-GOP-000245, *"Phenix Initial Lab Investigation (ILI) Process"*, Version: 4.0, Effective July 07, 2020 that provides instructions for processing the Initial Laboratory Investigations (Phase I) in the Phenix Initial Laboratory Investigation (ILI) workflow. This procedure also ensures appropriate root cause analyses, impact assessments. This system applies to the investigation of reportable results that are Out-of-Specification (OOS)/Out-of-Limit (OOL)/Out-of-Trend (OOT) or atypical for raw materials, in-process samples, in-process control limits (e.g., percent recovery), product intermediates, DS, DP, and stability samples. This procedure also includes the decision making procedure to perform a further phase 2 investigation and description of procedures to open a phase 2 investigation. The phase 2 investigation is governed by deviation procedure BQ-GOP-000248.

BQ-GOP-000246 provides detailed instructions for conducting an investigation of all Laboratory Events (LEs). Overall, the firm's procedures for OOS investigation conforms to the FDA guidance for Industry-Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production.

There were six OOS results related with (b) (4)-IC, three from the Chemistry QC Laboratory and the other three from the Microbiology QC Laboratory. The three OOS results from the Chemistry QC laboratory were reviewed as follows:

FRAD19L00020: OOS Concentration result 1 Week Accelerated Stability Time Point for (b) (4) ICB lot (b) (4). This event resulted in Deviation **FRAD19E0267**. On Sep 03, 2020, I (YXF) discussed this deviation with Mr. Derek Pandolfo, Sr. Manufacturing Manager. He explained that the root cause of this OOS was a sample that was not representative of lot (b) (4). The concentrations of initial and 1 month time points were within the specification. No CAPA was created.

FRAD19L00021: OOS Peptide Map Peak (b) (4) (Peak Ratio (b) (4) %) for (b) (4) lot (b) (4). This OOS result occurred on Aug 08, 2019. The root cause was determined to be use of the Zeba Spin desalting column in the assay. The CAPA was to revise the assay procedure FBL-MTD-000071 for instructions on inspection of the Zeba Spin columns prior to desalting and revise FBL-MTD-000071 to prepare the co-mix for samples prior to desalting. The investigation and CAPA were adequate.

FRAD20L00002: Specific Activity Result Generated for (b) (4) ICB Drug Substance Lot (b) (4). On Jan 20, 2020, QC Chemistry obtained an OOS Specific Activity result at 3 month (6 - 10°C) sample of (b) (4) ICB Lot (b) (4). The calculated result was (b) (4) U/mg (round to (b) (4) U/mg), which is outside of the specification of (b) (4) U/mg, whereas the Working Standard (WS) Lot (b) (4) included in the assay had a Specific Activity result of (b) (4) U/mg, which also failed to meet the specification of (b) (4) U/mg.

After review of the OOS document [**Exhibit YXF-13**], the root cause of the OOS was unclear. On Sep 4, 2020, I discussed this OOS with Mr. (b) (6), Principle Analyst; he explained that the root cause was that the concentrations of (b) (4) and (b) (4) were swapped in calculation of the specific activity. After the calculation was repeated with correct concentrations, the activity results for both samples were within specification. I expressed my concern on the unclear documentation to the management team. The firm acknowledged the problem and the partial reason is the Phenix system which is used to generate the reports. They are in a process to replace this system.

On Sep 03, 2020, I reviewed all failed tests in the QC Chemistry Laboratory for the testing of batches manufactured at 8 NYA. A total of 11 assays failed, among them, 9 were system suitability failure, 2 were lace box interruptions. The investigation and documentation of these laboratory events were acceptable.

No objectionable observation was identified.

Data Control

This section written by YXF

I reviewed FBL-SOP-000881, Version 12.0, effective Jun 08, 2020, a procedure for systematic review and sign-off of analytical data generated in the QC Laboratories. I reviewed the laboratory records for RP-UPLC purity test and the specific activity test for all three PPQ batches (b) (4). All results in the laboratory reports are consistent to the data in the (b) (4)

No objectionable observation was identified.

Analyst Training

This section written by YXF

All analysts involved in (b) (4) ICB are required to have appropriate training, which includes prerequisite courses covering basis laboratory skills such as pipetting, analytical balance use, and other general laboratory rules and On-job-training for each assay that the analyst will perform. I reviewed FBL-OJT-000213 for Activity Assay OJT and checked (b) (6) training record for the

Activity Assay and his training profile that included all training he has taken in the QC Laboratory. The training program of the firm is well designed, organized, and documented.

No objectionable observation was identified.

Sample handing and Shipping

This section written by YXF

On Aug 31, 2020, Mr. Mark Roy, QC Director, provided an overview of sample receipt, reserve, and retain. I reviewed SOPs that govern sample handing listed below:

- FBL-SOP-000964: *"Control Sample Receipt"*, Version 7.0, effective date Jul 28, 2020.
- FBL-SOP-001284: *"Sampling and Preparation of Integrated Continuous Biomanufacturing (ICB) samples from 8 NYA for Viral and Mycoplasma Testing"*
- FBL-SOP-000543: *"Reserve and Retain Program"*
- FBL-SOP-000172: *"Transport of Samples Between Buildings at the Framingham Campus"*
- Transfer and Transportation of Frozen Vials Utilizing (b) (4) Shippers

No objectionable observation was identified.

Laboratories (Microbiology)

This section written by WS

On 01 September 2020, I proceeded to the (b) (4) floor of Building 68 NYA, Bioburden Lab. Within the (b) (4) F16089 LF, I observed a mock (b) (4) sample test by (b) (4) method. I observed the hood sanitized with (b) (4), starting from the back wall, sides, work surface and front glass, along with the manifold and materials entering the LF. The (b) (4) contact time was timed. The technician donned new gloves and sterile sleeve guards for testing, with gloves frequently sanitized. I reviewed the procedure for test FBL-SOP-0019, *"Preparation and Incubation of Samples for Bioburden Determination at the 68 NYA Facility"*, v10, Effective date 16/07/20. The observed (b) (4) process was standard and acceptable. Observed within the area was logbooks 2019QCM0219, F-17173 (Temperature Log Sheet); 2019QCM0124, F-17174 (Dry Storage Checklist for Waterbath); and 2019QCM0220, F-17174 (Temperature Log Sheet 2 Waterbath). Each logbook was incomplete for secondary review, see **Exhibit WS-13.** Furthermore, a Sartorius analytical balance F-16499 located in an associated lab was determined not to be certified to USP 41 for analytical weighs supporting (b) (4) testing, see Exhibit **WS-Exhibit 15.**

I visually inspected the 30 - 35°C (b) (4) 4775 for bioburden sample incubation (b) (4), 20 - 25°C chamber 4765 for routine EM and media fill testing, and cold room 4745 for 2 - 8°C reagent storage.

I observed endotoxin testing, mock (b) (4) test according to USP 85 and procedure FBL-SOP-000871, *"Determination* (b) (4) ELx808 plate reader for testing was certified May 2021, with quality calibration plates (3 available) in verification of system performance that were in a state of certification. I observed the technician log onto the ELx808 system (computer) with a unique user name and password. I request the technician to right click on a data file, with the option to delete the file restricted.

This resulted in a 483 Observation and is additionally discussed under Objectionable Conditions 2.a and b, Section X.

Instrument Qualification, Calibration, Maintenance and Methods

This section was written by WS

Instrument Qualification:

On 03 September 2020, Mr. Jason Fahy, QC Associate Director and Mr. (b) (6), Metrology Operations Support Group Lead provided an overview of compliance with USP 41 for analytical weighs. I reviewed SOP FBL-SOP-000555, *"Calibration and Documentation for the Mettler Toledo XP205 and XPE205 Analytical Balance"*. The procedure is for a (b) (4) weight check. I reviewed FBL-SOP-000580, *"Calibration and Documentation for the Mettler XP56 Microbalance"*. Again, the procedure is used in support of (b) (4) weight checks. The balances were initially certified and (b) (4) thereafter by Mettler. Mettler performs the USP 41 certification as well as Genzyme. The Sartorius balance F16499 used in analytical weighs for (b) (4) has not been certified to USP, see **Exhibit WS-15** On the 04 September 2020, the firm provided Work Report FRAD20E0760 (see **Exhibit WS-16**) for certification of the balance to USP-41 and the certification by Genzyme conducted 03 September 2020 as it relates to the inspection concern, see **Exhibit WS-17.**

This resulted in a 483 Observation and is additionally discussed under Objectionable Conditions 2.a, Section X.

On 04 September 2020, Mr. (b) (6), Validation Manager, Mr. Brian Donohue, Associate Director of QC Microbiology, and Mr. (b) (6), Manager of Automation provided an overview of controlled temperature units. I reviewed final report for the (b) *"Installation Qualification of Warm Room 4775 at 68 NYA Study 21-0052"*, 26 July 2012. The IQ was standard in design. I reviewed Amendment #1 to the final report for the *"Installation Qualification of Warm Room 4775 at 68 NYA"*, 18 October 2012, Study 21-0052. The amendment addressed discrepancies in the IQ. I reviewed the *"Operational Qualification of the Warm Room 4725 at 68 NYA"*, July 2012. The OQ was standard and included one empty chamber study, (b) (4) thermocouples positioned geometrically with 30 - 35°C temperature control maintained. I reviewed the Performance Qualification 21-0054, *"PQ of the Warm Room 4775 at*

68 NYA", 12 October 2020. Testing included a loaded chamber, chamber recovery, and material addition. The loaded chamber included (b) (4) geometrically placed thermocouples over (b) (4), with Run 1 and 2 rejected based on the thermocouples not being stabilized at study start, a protocol requirement. Run 3 was acceptable for 30 - 35°C temperature control, with the 2019 - 2020 trend data acceptable.

I reviewed the RQ, *"Protocol for the 2018 Requalification of the QC Microbiology Warm Room 4775 (F-15594 Located at 8 NYA), Sanofi Genzyme 68 NYA Framingham 21-0475"*, 24 September 2018. Testing included alarms, loaded chamber distribution profile using (b) (4) thermocouples over (b) (4). 30 - 35°C temperature control was confirmed.

I reviewed the 20 - 25°C (b) (4) ambient room under protocol, *"Installation Qualification of the Warm Room 4765 at 69 NYA 21-0048"*, 23 September 2011. The IQ was standard in design. I reviewed study 21-0048, *"68 NYA Ambient #1 to the IQ of Warm Room 4765 at 69 NYA"*. The amendment supported IQ discrepancy resolutions consisting of utility discrepancies. I reviewed the *"Operational Qualification of the Warm Room 4765 at 69 NYA"*, 21-0049. The OQ included alarm testing and empty chamber distribution study using (b) (4) thermocouples positioned geometrically for (b) (4), with 20 - 25°C temperature control maintained. I reviewed 21-0049A1, *"Amendment #1 to the Final Report for the Operational Qualification of the Warm Room 4765 at 68 NYA"*, with the amendment to address discrepancies. I reviewed the protocol for the *"Performance Qualification of the Warm Room 4765 at 68 NYA"*, that included loaded chamber, addition to loaded chamber and recovery. (b) (4) thermocouples were positioned for (b) (4) (b) (4), with 20 - 25°C temperature control maintained. The temperature trend data for 2019 - 2020 was acceptable.

I reviewed the *"Protocol for the 2018 Requalification of the QC Microbiology Warm Room 4765 (F-1559) located at 68 NYA (V-0194) Sanofi Genzyme, 68 NYA, Framingham 21-0472"*, September 2018. Testing included alarms, with (b) (4) thermocouples positioned geometrically and as penetration probes for (b) (4), with 20 - 25°C temperature control maintained.

I reviewed the 2 - 8°C laboratory upright refrigerator used in reagent storage under 21-0039, *"Final Report for the Installation Qualification of Cold Room 4745 at 68 NYA and Protocol for the Installation Qualification of the Cold Room 4745 at 68 NYA 21-0039"*, November 2011. The Installation Qualification was standard in design. I reviewed *"Amendment #1 for Final Report for the Installation Qualification of Cold Room 4745"*, with the amendment addressing discrepancies. I reviewed *"Protocol for the Operational Qualification of the Cold Room 4745 at 68 NYA"*, 21-0040. The OQ included alarm testing and empty chamber distribution profile, with (b) (4) thermocouples positioned geometrically for (b) (4), with 2 - 8°C temperature control maintained. I reviewed *"Protocol for the Performance Qualification of the Cold Room 4745 at 69 NYA"*, 21-0041, 10 May 2012. The PQ included a loaded chamber, material addition and recovery. A geometric distribution profile of the chamber over (b) (4) indicated 2 - 8°C temperature control. I reviewed the 2019 - 2020 trend data, with 2 - 8°C temperature control maintained. A secondary backup probe was determined to be faulty, with the firm to initiate a work request as corrective action.

I reviewed Study 20-1263, *"Quality System Review and Physical Testing Requalification of Cold Room 4745 (V-0170) at 68 NYA Framingham Biologics"*, May 2019. Testing included alarms, with (b) (4) thermocouples positioned geometrically and as penetration probes for (b) (4), with 2 - 8°C temperature control maintained.

Methods: On the 28 August 2020, Mr. Armin Opitz, Director of Manufacturing Science, Ms. (b) (4), Principle Quality Engineer, Ms. (b) (6), QC Scientist II, Ms. (b) (6), Process Engineer Senior, Mr. (b) (6), QC Scientist, Mr. (b) (6), QC Analyst Principle, and Mr. Brian Donohue, Associate Director of QC Microbiology provided an overview of the method validation for endotoxin, with compendial method verification performed for the kinetic turbidimetric and chromogenic (plate), and kinetic chromogenic for the Nexus system. The lab supporting testing at 68 NYA has not changed since the first generation (b) (4), with the lab responsible for IPC, water and drug substance testing. Some endotoxin method validations were reperformed based on the generation 2 formulation (new (b) (4)), equipment and IPC testing (sample (b) (4)). Drug substance method validation was not reperformed based on the drug substance considered equivalent.

Regarding (b) (4), plate based, I reviewed the *"Final Report for Bacterial Endotoxin Test, USP <85> Method Verification of* (b) (4) *ICB* (b) (4) *in the QC Microbiology Laboratory FBL-RPT-00192"*, v1.0, Effective date 29/10/2018. Testing included (b) (4) identified under Table 1 of the document, see **Exhibit WS-18**, with testing according USP <85> turbidimetric, where the maximum validated dilution (MVD), interference screening, and (b) (4) - (b) (4) % recovery was assessed and acceptable.

I reviewed FBL-RPT-000216, *"Final Report for the Bacterial Endotoxin Test USP <85> Method Verification of* (b) (4) *ICB* (b) (4)*, Media, and In-process Samples using* (b) (4) (b) (4) *Based Technology"*, V1, Nexus System. Testing was according to USP <85> for (b) (4), media and IPC samples, with method verification supporting (b) (4) - (b) (4) % Recovery.

I reviewed the Nexus System for drug substance under FBL-RPT-000352, *"Final Report for the Bacterial Endotoxin Test USP <85> Method Verification of* (b) (4) *Formulated Drug Substance using* (b) (4) *Based Technology"*, v1.0, Effective date 12/03/2019. pH was controlled with recoveries (b) (4) - (b) (4) % recovery. I reviewed IPC testing under FBL-RPT-00216 for the Nexus System, with results acceptable.

I reviewed FBL-RPT-000367, *"Final Report for Bacterial Endotoxin Test, USP <85> Method Validation Verification of* (b) (4) *ICB* (b) (4) *Liter Bioreactor in QC"*, v1.0, Effective date 26/04/2019. The process was plate based for the (b) (4) liter bioreactor IPC samples, with (b) (4) - (b) (4) % recoveries. I reviewed the downstream (b) (4) under 18 TRF-009, *"Final Report for the Method Verification of USP <85> Bacterial Endotoxin Test for* (b) (4) *ICB In-process Samples"*. Recoveries were (b) (4) - (b) (4) %. Report FBL-RPT-00958 included an addendum to the endotoxin limit, *"Addendum to Final Report for the Method Verification of USP <85> Bacterial*

Endotoxin Test, for (b) (4) *ICB In-process Samples Addendum 18TRF009*", v1, Effective date 09/07/2020. Recoveries were (b) (4) - (b) (4) %.

Bioburden: Bioburden method verification was performed for IPC (new material testing) and new (b) (4), with testing by (b) (4) and spread plate. I reviewed FBL-RPT-000188, *"Final Report for the Bioburden Verification of* (b) (4) . Testing included ATCC organisms and 3 house isolates, with 3 batches verified with recoveries (b) (4) - (b) (4) %, acceptable.

I reviewed TR No. 17TRF021, *"Final Report for Bioburden Method Verification of* (b) (4) *ICB* (b) (4) *in the QC Microbiology Laboratory"*. Organisms included *S. aureus* ATCC 6538, *P. heruginosa* ATCC 9027, *B. subtilis* ATCC 6633, *C, albicans* ATCC 10231, *A. brasliennis* ATCC 16404, *Kocuria rhzophillia, Relstonia pickettii,* and *Aspergillus versicolor* bioball, plant isolates. Media assessed included (b) (4) One isolate required incubation to (b) (4), with all recoveries (b) (4) - (b) (4) %.

I reviewed FBL-RPT-00027, *"Final Report for Bioburden Method Verification of* (b) (4) *ICB In-Process Samples in the QC Microbiology Laboratory"*, v1, Effective date 22/10/2018. Samples included (b) (4) Some of the IPC samples had anti-microbial properties, with a (b) (4) mL flush with fluid (b) in mitigation. All three studies passed, with the exception of (b) (4) with recoveries for *Pseudomonas aeruginosa, Bacillus subtilis* having recoveries below (b) (4) %. The method is used as-is, with method associated with an information request by the Agency.

I reviewed *"FBL-RPT-000308, Bioburden Method Verification for* (b) (4) (b) (4) *"*, v1, Effective date 06/03/2019. Three studies were performed with *B. subtilis, C. albicans, A. brasiliensis, S. aureus, P. aeruginisa,* and isolates, with recoveries (b) (4) - (b) (4) %. I reviewed FBL-RPT-000336, *"Final Report for the Bioburden Verification of* (b) (4) *"*. Three studies were performed as prior with recoveries (b) (4) - (b) (4) %. I reviewed FBL-RPT-000337, *"Final Report for the Bioburden Verification of* (b) (4) *liter Bioreactor"*. Recoveries were > (b) (4) % for *Psudomonas aeruginosa* in (b) (4) media. A deviation investigation was conducted, with detectability enhanced and acceptable.

Reference Discussion Item WS-2 in Section XII, GENERAL DISCUSSION WITH MANAGEMENT.

OOS Procedure and Investigations

This section was written by WS

On 31 August 2020, Mr. (b) (6), Principle Quality Engineer, Mr. Timothy McKendry, Associate Director QC Compliance and QC Technical Management Support, and Mr. Sean O'Brien, Director Quality Contamination Control provided an overview of the investigational process for an OOS under procedure BQ-GOP-000245, *"Phenix Initial Laboratory Investigation Process"*, v4, Effective date 15/07/2020. OOS investigations are conducted under a phase approach: Phase 1 is a review of the laboratory analyst. If a definitive root cause is identified for the OOS, the Phase 1 review is sufficient. A phase 2 review is conducted when a definitive root cause is unknown and includes a cross functional investigation, sample process review, other contamination, and also looks at product impact. A retest is based on a deviation investigation at the OOS level, with retest protocol required and approved by the director of QA. A Phase 1 investigation is conducted within (b) (4), with Phase 2 conducted within (b) (4) from date of discovery.

For any bioburden hit, an I.D. is performed with investigation. On 03 September 2020, I reviewed the following OOS:

FRAD19L00012: Opened 2 July 2019, Closed 19 July 2019. The OOS was for a cleaning verification sample for the (b) (4), (b) (4) CFU/100 mL, acceptance limit < (b) (4) CFU/100 mL. This was not a lab issue, with *R. pickitti* the source of the bioburden. A Phase 2 investigation was conducted, with the root cause associated with (b) (4) the (b) (4), with the manual rinse and floor drain manipulated with gloved hands. Gloves were not changed in the sampling process causing the contamination. A CAPA was completed to mitigate a future occurrence.

FRAD192L0007: Opened 22 June 2019, Closed 03 July 2019. The OOS is associated with media lot (b) (4) post filtration bioburden failure, with the root cause, sample acquisition for bioburden compromised by operator, with resample taken prior to production and acceptable.

No objectionable observation was identified.

IX. Objectionable Conditions Prior Inspection and Resolutions

The prior inspection was classified NAI.

X. Objectionable Conditions and Management's Response

Observation 1:

Observation 1: Facilities and equipment supporting manufacture are not adequately maintained. Specifically,

a. On September 2, 2020, (b) (4) FB-2880-001 used in sterilization of the (b) (4) filter and bioreactor probes was observed with (b) (4) and (b) (4) residue on

the (b) (4) cart. The (b) (4) chamber was also observed in a similar condition. There is no routine inspection of the (b) (4) for cleanliness nor is there a procedure for cleaning.

b. On August 26, 2020, an air return pre-filter located within Downflow Booth DFB1000001 used in raw material weighing, was observed not secured to its mounting. The filter is a pre-filter to the high efficiency filter and subsequent downflow booth ceiling HEPA filter bank.

c. A ceiling air supply diffuser screen in Suite (b), CNC space was observed not secured to its ceiling mount. The cause was an unsecured fastener. Numerous other air supply diffuser screens within the CNC space were observed with similar unsecured fasteners.

Supporting Evidence and Relevance Observation 1.a: Regarding the (b) (4) FB-2880-001 used in bioreactor probe and (b) (4) filter sterilization, (b) (4) was observed on the (b) (4) cart, along with a similar condition for the chamber, see **Exhibit WS-7**. There is no procedure for routine inspection of the (b) (4) nor is there a procedure for cleaning.

Management's Response: On 03 September 2020, Mr. Kyle Bigness, Sr. Manager (b) (4)-ICBF Project provided a follow up to the observed (b) (4) cart and chamber condition. There is no routine inspection of the (b) (4) and there is no procedure for cleaning of the (b) (4). Corrective action included Work Order 2609026 for investigate and repair stains on the inside of the (b) (4) and cart, see **Exhibit WS-9** and Work Order 2608722, Lock-out (b) (4) and remove residual (b) (4) inside the unit, see **Exhibit WS-10.** The firm will implement or update a procedure for routine inspection and cleaning of the (b) (4). Pictures were provided by the firm, with the residual (b) (4) removed from the (b) (4) cart and chamber, see **Exhibit WS-11.**

Supporting Evidence and Relevance Observation 1.b: The weigh and dispense area contains (b) (4) downflows with 100% HEPA filter coverage. Observed was a return filter to the high efficiency filter not secured to it mounting in downflow booth DFB1000001, see **Exhibit WS- 5.** The filter is a pre-filter to the high efficiency filter and subsequent downflow booth ceiling HEPA filter bank.

Management's Response: On 03 September 2020, Mr. Bill Culleton, Sr. Director Facility Operations provided Work Report FRAD20E0729, event record date 27 Aug 2020 for reseating of the filter into its holder, see **Exhibit WS-4.**

Supporting Evidence and Relevance Observation 1.c: In CNC space, ceiling diffuser screens were observed not securely attached to ceiling mounts. The cause was associated with unsecured fasteners, see **Exhibit WS-3.**

Management's Response: On 03 September 2020, Mr. Bill Culleton, Sr. Director Facility Operations provided a follow up for the diffuser screens, fasteners becoming loose over time. All were tightened according Work Report FRAD20E0729, 27 Aug 2020, see **Exhibit WS-4.**

Observation 2: Equipment used within the QC Microbiology Laboratory has not been adequately certified and review of logbooks has not been conducted according to procedure. Specifically,

a. Sartorius analytical balance F-16499 has not been certified in determination of the balance minimum weigh amount.

b. Standard operating procedure FBL-SOP-000942, Good Documentation Practices, v6, Effective date 01/09/2020 identifies under section 6.10.9 that functional area review of logbooks is to be conducted within (b) (4) of final entry. The following logbooks located within the bioburden room exceeded the (b) (4) specification:

   i. Logbook 2019QCM0219, Equipment I.D.: F-17173, Temperature Log Sheet 2, Water Bath.
   ii. Logbook 2019QCM0220, Equipment I.D.: F-17174, Temperature Log Sheet 2, Water Bath.
   iii. Logbook 2019QCM0124, Equipment I.D.: F17174, Dry State Storage Checklist for QCM Water Baths.

Supporting Evidence and Relevance Observation 2.a: The Sartorius balance F16499 used in analytical weighs for (b) (4) has not been certified to USP, see **Exhibit WS-16.**

Management's Response: The firm certified the balance to USP 41 03 September 2020, see **Exhibit WS-17.**

Supporting Evidence and Relevance Observation 2.b: Observed within the bioburden lab area were logbooks 2019QCM0219, F-17173 (Temperature Log Sheet); 2019QCM0124, F-17174 (Dry Storage Checklist for Waterbath); and 2019QCM0220, F-17174 (Temperature Log Sheet 2 Waterbath) not reviewed according to SOP FBL-SOP-000942, *"Good Documentation Practices"*, v4, Effective date 01/09/2020, **Exhibit WS-12.** Each logbook was incomplete for secondary review, see **Exhibit WS-13.**

Management's Response: Deviation FRAD20E0749 was opened, with the root cause inadequate procedure, see **Exhibit WS-14.** The logbooks were closed, with new logbooks issued, and new process to eliminate the reoccurrence of the objectionable condition. Logbook will transition to LIMS for efficiency and control purposes.

XI. Refusals

No refusals were encountered during the inspection.

XII. General Discussion with Management

Discussion Item WS-1: The (b) (4) is stored in (b) (4). The (b) (4) exchange includes (b) (4) followed by bioburden and endotoxin testing. In a discussion with the firm, taking the bioburden and endotoxin sample at pre-(b) (4) from the (b) (4) or (b) (4) may offer an enhanced understanding for bioburden and endotoxin control.

Discussion Item WS-2: In review FBL-RPT-000337, *"Final Report for the Bioburden Verification of* (b) (4) *ICB* (b) (4) *liter Bioreactor"*, recoveries were > (b) (4) % for *Psudomonas aeruginosa* in (b) (4) media. A deviation investigation was conducted, with detectability enhanced and acceptable. The firm was reminded of the growth promoting capabilities of the media.

Discussion Item WS-3: I reviewed CAPAs in mitigation of the false TOC positives from the WFI system, with a CAPA from February 2019 completed 2020 for how samples are taken in mitigation of (b) (4) contamination. The process for sampling includes acquisition of the TOC, conductivity and nitrate samples, followed by (b) (4) application and acquisition of the bioburden and endotoxin samples. An additional CAPA FRAD19A0094, Opened October 21, 2019, Closed February 14, 2020 suspected the use of (b) (4) as the cause of the false positives, with a focus on sampling technique. New CAPA FRAD20A0315 opened August 18, 2020 has been initiated for sampling and training for sample acquisition consistency, and FRAD20A316 for time for WFI dispense, limited (b) (4) application, and process for sanitization of gloves. Both CAPAS were initiated based on an adverse trends in TOC. The firm is adding an attachment to the WFI sample port to reduce flow in support of sample acquisition, with the attachment a possible contributing factor under review for the false TOC positives. I reminded the firm that the period of time in resolving the false positive TOC results was less than optimum. The firm understood the issue.

Discussion Item WS-4: Regarding WFI, water testing started in April 2019, with (b) (4) points of use tested (b) (4) for bioburden, endotoxin, TOC, conductivity and nitrates. The (b) (4) data for bioburden was acceptable, with endotoxin having 9 alert level excursions, points of use (b) (4) and (b) (4). The locations for the endotoxin excursions were at the WFI supply to the storage tank from the (b) (4). The (b) (4) data indicating low levels of endotoxin from the (b) (4), with carryover from the pre-treatment system as determined from FRAD19E0495, opened November 2019, closed June 2020. From an engineering protocol, sampling identified elevated levels of endotoxin from the (b) (4) June 2019 and May 2020, with CAPA FRAD20A0220 changing the sanitization frequency from (b) (4) to (b) (4). An engineering protocol implemented August 24, 2020 includes (b) (4) sampling from (b) ports for endotoxin: (b) (4) Testing at the (b) (4) valves post (b) (4) and prior to the WFI entering the tank

indicated the absence of detectable levels of endotoxin. Change control 19FRACC0032 has been implement for routine testing of the pretreatment system in support of assuring system performance for endotoxin control. I reminded the firm that the period of time in resolving the elevated endotoxin levels from the pretreatment system was less than optimum.

Discussion Item WS-5: Per BQ-GOP-00008, *"Establishing and Maintaining Quality Agreements"*, v5, Effective date 21 May 2019, Quality Agreements should be reviewed within (b) (4). Three quality agreements were past due and did not have CAPAs. The firm indicated that the past due quality agreements would be identified as late in the annual PQR. I reminder the firm of the importance of following procedures and meeting the written goal.

Discussion Item WS-6 Regarding deviation investigation FRAD19E0013: Opened May 22, 2019, Closed July 25, 2019. A settling plate under dynamic conditions within the seed LFCB had a recovery of (b) CFU, acceptance criteria < (b) CFU. The technician associated with the recovery may not always be informed of the event, as for the technician to take an accounting of their aseptic technique. The firm was reminded that perhaps the technician should always be informed of the events.

XIII. Additional Information

None.

XIV. Samples Collected

No physical samples were collected.

XV. Voluntary Corrections

None.

XVI. Exhibits Collected

Exhibit WS-1: Sanofi, 8 NYA-(b) (4) ICB PAI Opening Presentation 26 August 2020, 35 Pages.
Exhibit WS-2: 2020 FDA PAI Inspection, Personnel Interaction with Inspectors and Opening and Close Meeting, 20 Pages.
Exhibit WS-3, Pictures of CNC Diffuser Screens, 5 Pages.
Exhibit WS-4, Work Report FRAD20E0729, Multiple (2) Observations Identified During Walkthrough of 8 NYA Facility, 3 Pages.
Exhibit WS-5, Picture of Pre-Filter, 1 Page.
Exhibit WS-6, Work Order 2808649 and Work Report FRAD20E0730, Multiple (3) Observations Identified in Mechanical Room 1170 at 8 NYA on FDA PAI Tour, 12 Pages.
Exhibit WS-7, (b) (4) Pictures, 6 Pages.
Exhibit WS-8, SOP FBL-EWI-000005, Facility and Equipment Disinfection, Effective date 20/05/2020, 63 Pages.

Exhibit WS-9, Work Order 2609026, Investigate and Repair Staining on the Inside of the (b) (4) and Cart, 4 Pages.
Exhibit WS-10, Work Order 2608722, Lockout (b) (4) and Remove Residual (b) (4) Inside Unit, 4 Pages.
Exhibit WS-11, (b) (4) Chamber and Cart Pictures, 9 Pages.
Exhibit WS-12, SOP FBL-SOP-000942, Good Documentation Practices, v4, Effective date 01/09/2020, 33 Pages.
Exhibit WS-13, Logbook 2019QCM0124, 2019QCM0220, and 2019QCM0219, 57 Pages.
Exhibit WS-14, Work Report FRAD20E0749, Multiple (3) Logbooks Identified with Review Not Meeting (b) (4) Target for Review per FBL-SOP-000942, 6 Pages.
Exhibit WS-15, Sanofi Certificate of Calibration, Metrology ID# F-16499, Analytical Balance, 8 Pages.
Exhibit WS-16, Work Request FRAD20E0760, F-16499 Not Calibrated in Accordance with USP 41, 6 Pages.
Exhibit WS-17, Sanofi Certification of Analytical Balance F-16499 to USP 41, 2 Pages.
Exhibit WS-18, SOP FBL-RPT-000192, Final Report Bacterial Endotoxin Test <85> Method Validation of (b) (4) ICB (b) (4) in the QC Microbiology Laboratory, v1.0, Effective date 29/10/2018, 24 Pages.
Exhibit YXF-1: List of Equipment OOT, 2 Pages.
Exhibit YXF-2: Batch record design presentation, 8 Pages.
Exhibit YXF-3: Electronic Batch Record technical support slides, 4 Pages.
Exhibit YXF-4: Sportfire Characterization Data, 25 Pages.
Exhibit YXF-5: (b) (4) Chromatograms for the PPQ run, 3 Pages.
Exhibit YXF-6: Lot list manufactured at 8 NYA, 2 Pages.
Exhibit YXF-7: Process diagram fro (b) (4) -ICB at 8 NYA, 1 Page
Exhibit YXF-8: Gowning Procedure in response to Covid 19, 8 Pages.
Exhibit YXF-9: Framingham Covid 19 Safety Assessment, 3 Pages.
Exhibit YXF-10: Multiproduct control presentation, 8 Pages.
Exhibit YXF-11: F008-ED-GNRL-0386, Multiproduct manufacturing at ICBF at 8 NYA, 12 Pages.
Exhibit YXF-12: Stability &Statistics- Assay control Extension for (b) (4) ICB Aggregation Method, 6 Pages.
Exhibit YXF-13: ILI FRAD20L00002, Out of Specification (OOS) Specific Activity result generated for (b) (4) ICB Drug Substance Lot (b) (4), 6 Pages.

XVII. List of Attachments

Attachment 1: Form FDA 483, 2 Pages.
Attachment 2: Form FDA 482, 3 Pages

XVIII. Signatures

Wayne E. Seifert -S

Digitally signed by Wayne E. Seifert -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001593284, cn=Wayne E. Seifert -S
Date: 2020.10.14 08:58:48 -04'00'

Wayne Seifert
Consumer Safety Officer
CDER/OPQ/OPMA/DBM1

Ying Xin Fan -S

Digitally signed by Ying Xin Fan -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ying Xin Fan -S, 0.9.2342.19200300.100.1.1=2000604371
Date: 2020.10.14 09:15:30 -04'00'

Ying-Xin Fan
Chemist
CDER/OPQ/OBP/DBRRIV