TABLE OF CONTENTS

SUMMARY

(Written by Investigator Marcsisin)

This pharmaceutical inspection of Genzyme Corporation, Framingham, MA, a manufacturer of therapeutic bulk drug substances intended to be used in sterile injectable drug products, was conducted in accordance with Compliance Program 7356.002M, Inspection of Licensed Biological Therapeutics Drug Products, and guidance contained in ICH Q7A, Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients under operation ID: 178869 and FACTS Assignment ID: 12223279, as part of the OPQO Pharm Division-1 FY 22 work plan and to cover cell bank manufacturing activities at 76 New York Avenue for the European Medicines Agency request. The FDA site dossier generated for this assignment can be found in **Attachment 4**.

According to management the firm continues to manufacture Thyrotropin alfa (Thyrogen, BLA 20-898), Agalsidase beta (Fabrazyme, STN BL 103979), and Imiglucerase (Cerezyme, BLA 20-367) bulk drug substances used for the production of finished drugs for commercial distribution in the United States.

The previous FDA inspection of the firm was a pre-approval inspection conducted from 8/26/2020-9/4/2020. The previous inspection was conducted to support the approval of Genzyme Corporation

Biologic License Application Supplement (BLA 103979/S5310) for Fabrazyme (Agalsidase beta) drug substance manufacture at 8 New York Ave. (NYA), Suite 1. A 2-item Form FDA 483-Inspectional Observations, was issued to Lisa McClintock – Site Head Framingham Biologics, for the following deficiencies:

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.

The previous FDA inspection was classified as Voluntary Action Indicated (VAI). The firm's corrective actions to the previous Form FDA 483 were covered during the current inspection and appeared to adequately address the observations.

The previous FDA routine surveillance inspection of the firm was conducted from 1/23/2017-2/2/2017. A Form FDA 483 was not issued at the close of the previous surveillance inspection and the inspection was classified as "No Action Indicated" (NAI).

The current inspection focused on the firm's Quality, Production, Facilities and Equipment, and Laboratory Systems supporting commercial manufacture of the biologically derived drug substance (BDS) Thyrogen, BLA 20-898. Operations within buildings (b) (4) NYA (main Thyrogen manufacturing area), (b) (4) NYA (cell bank storage, Thyrogen buffer preparation, QC chemistry laboratory), (b) (4) NYA (GMP warehouse and BDS shipping/preparation area), (b) (4) NYA (back-up cell bank storage), and (b) (4) NYA (previous location of cell bank manufacturing activities) were covered during the current inspection. The current inspection concluded on 7/25/2022, with the issuance of a 2-item Form FDA 483 to Larry Yudiski - Head of 8 New York Avenue Manufacturing and Interim Site Head, for the following deficiencies:

1. Failure to exercise sufficient controls over computerized systems and failure to have adequate controls to prevent omission of data.
2. Failure to properly maintain buildings and facilities used in the manufacture of bulk drug substances.

Mr. Yudiski stated that the firm would respond in writing to the inspectional observations.

No samples collected during the current inspection.

ADMINISTRATIVE DATA

Inspected firm:	Genzyme Corporation
Location:	31,45,49,51,55,68,74,76,80 New York Ave. Framingham, MA 01701-8861
Phone:	800-326-7002
FAX:	508-872-9080
Mailing address:	68 New York Ave Framingham, MA 01701-8861
Email address:	

Dates of inspection: 7/18/2022-7/22/2022, 7/25/2022
Days in the facility: 6
Participants: **Sean R Marcsisin, Investigator**
Daniel L Zheng, Investigator

(Written by Investigator Marcsisin)
On 7/15/2022, I called Darren Marino – Associate Director of Quality, to inform the firm and pre-announce the FDA inspection. Mr. Marino instructed me to call the firm's main security line. I called the firm's security line and spoke with Wanice Matthews – Security Supervisor. I informed Ms. Matthews of the inspection and she stated that she would let site management know. Later that day, Gary Dodakian – Senor Director, Quality, called me and I confirmed with him the FDA inspection start date of 7/18/2022.

On 7/18/2022, Investigator Daniel Zheng and I (Sean Marcsisin), presented our credentials and issued a "Form FDA 482, Notice of Inspection" (**Attachment 1**) to Larry Yudiski - Head of 8 New York Avenue Manufacturing and Interim Site Head. Mr. Yudiski indicated that he was the most responsible person onsite at that time.

On 7/25/2022, we held an inspection closeout meeting and issued a 2-item Form FDA 483 to Larry Yudiski - Head of 8 New York Avenue Manufacturing and Interim Site Head. During the closeout meeting, firm management brought to our attention that the room number listed in **Observation 2**, 3rd and 4th bullet points (room 190) was incorrect and should be room 140. An amended Form FDA 483 was issued to Mr. Yudiski with the corrected room number while we were still on site.

Throughout this report, Genzyme Corporation. located at 68 New York Ave., Framingham, MA is synonymous with "Genzyme Corporation", "Sanofi", the "firm", and the various facilities of the Framingham site/campus (i.e., 31, 45, 49, 51, 55, 68, 74, 76, 80 NYA).

The terms "I" and "me" used in this report refer to the writer of the respective sections who are identified below the section heading or subheading.

HISTORY

(Written by Investigator Marcsisin)
The firm's Genzyme, Framingham site continues to operate as a division of Sanofi. The Framingham site is a multibuilding campus that has areas for bulk drug substance manufacture, warehousing, QC microbiology and chemistry laboratories, research and development activities, biosurgery product manufacture, and COVID-19 vaccine manufacture. Firm management provided an opening presentation that outlines the various activities conducted at the Framingham site (see **Exhibit 3**). Firm management also provided the Framingham site master file (see **Exhibit 4**). The firm's manufacture of bulk drug substances from biological origin at the Framingham site falls under the Framingham Biologics program. Framingham Biologics has approximately (b) (4) employees. The firm's core hours are Monday – Friday, 9 am to 5 pm. Manufacturing activities occur (b) (4) coverage and occur (b) (4) . The firm is currently registered with FDA (see **Exhibit**

5). The firm has two other sites located outside of Framingham, MA, that support product manufacture which are a warehouse located in Northborough, MA, and the fill/finish manufacturing site located in Waterford, Ireland. For the FDA registrations of the Northborough and Waterford sites, see **Exhibit 6**.

Post-Inspectional Correspondence/ FMD-145
FMD-145 correspondence should be directed to:
Larry Yudiski - Head of 8 New York Avenue Manufacturing and Interim Site Head
68 New York Ave
Framingham, MA 01701-8861
Lawrence.Yudiski@Sanofi.com

All other official correspondence should be directed to:
Paul Hudson – Chief Executive Officer
Sanofi-Aventis SA
54, Rue La Boétie, 75008
Paris, France
Paul.Hudson@Sanofi.com

INTERSTATE (I.S.) COMMERCE AND JURISDICTION
(Written by Investigator Marcsisin)
The firm continues to manufacture Thyrotropin alfa (Thyrogen, BLA 20-898), Agalsidase beta (Fabrazyme, STN BL 103979), and Imiglucerase (Cerezyme, BLA 20-367) bulk drug substances at the Framingham site. Bulk drug substances manufactured in Framingham, MA, are then sent to the Genzyme Ireland Limited site in Waterford, Ireland for fill/finish. The firm's finished drugs are then commercially distributed in the United States. Materials, components, and container closures utilized for BDS bulk drug substance manufacture are obtained from various suppliers located outside of the Commonwealth of Massachusetts.

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED
(Written by Investigator Marcsisin)
Firm management provided organizational charts for Genzyme Corporation and Sanofi during the current inspection (see pages 12-15 of **Exhibit 3**). Additionally, firm management provided a listing of firm employees who provided information during the inspection as well as inspection closeout attendees (see **Exhibits 7 & 8**).

(Written by Investigator Zheng)
During the inspection, the following individuals provided information related to their responsibilities:

Lawrence Yudiski, Head of 8NYA Manufacturing, Head of 8 NYA Manufacturing and Interim Site Head: Mr. Yudiski goes by Larry as his first name. Mr. Yudiski stated that he was the most responsible person at the firm and was issued the FDA 482 Notice of Inspection at the start of the inspection on July 18, 2022. Mr. Yudiski has been with the firm for 20 years, 1.5 in his current

position. He is responsible for directing the Framingham site's leadership team as well as for running manufacturing at the 8 New York Avenue (8NYA) site. Mr. Yudiski has (b) (4) direct reports, which he stated includes the manufacturing directors at 8NYA and project directors for development of new drug products. Mr. Yudiski reports to Franck Chassant, Head of Rare Disease, Oncology & Immunology Industrial Cluster. Mr. Yudiski has the authority to make personnel and financial decisions on behalf of the firm.

Gary Dodakian, Head of Quality Framingham Biologics: Mr. Dodakian has been with the firm in his current capacity since September of 2016, and 15 years with the firm overall. He is overall responsible for quality and compliance at the firm. Mr. Dodakian has (b) (4) direct reports and reports in turn to Brandon Varnau, Quality Head for Specialty Care. Mr. Dodakian has the authority to make personnel and financial decisions on behalf of the firm.

FIRM'S TRAINING PROGRAM

(Written by Investigator Zheng)

The firm's training program is governed by procedure BQ-GOP-000009 Training System for Specialty Care Operations Network. General training consists of new hire onboarding, annual training on cGMP principles, job-specific training, and training associated with changes to processes and procedures, which the firm refers to as (b) (4) training. Training courses can take the form of instructor-led, electronic modules, read and understand, and on-the-job training overseen by a qualified trainer. Course groupings known as (b) (4) Curricula, and curricula are assigned in full. The firm documents training records in the learning management software (b) (4).

The firm does not have pre-determined training requirements by position: assignment of curricula is at management discretion based on the processes that a particular operator will conduct on completion of training. Personnel may be exempted from training requirements at management discretion. According to Gary Dodakian, Head of Quality Framingham Biologics, this is generally reserved for exempting the author of a training course, and any exemption would be reviewed by the firm's Learning and Development (L&D) department. If personnel are disqualified from a procedure or process due to unsatisfactory performance, L&D may generate a Training Plan with input from QA and area management to retrain the employees. For assignment of annual training, L&D establishes and approves a "Network" Training Plan to outline for the next year any training on cGMPs or compliance based on emerging trends. L&D also operates a Trainer Qualification Program intended to ensure that personnel overseeing on-the-job trainings are qualified to do so.

During this on-site inspection, I reviewed the full training records for two experienced operators and two new operators without comment.

MANUFACTURING/DESIGN OPERATIONS

QUALITY SYSTEM

Conduct of the Inspection

(Written by Investigator Marcsisin)

The current inspection focused on the firm's Quality, Production, Facilities and Equipment, and Laboratory Systems supporting commercial manufacture of the biologically derived drug substance (BDS) Thyrogen, BLA 20-898. The inspection consisted of physical inspection of the firm's facilities and equipment, observation of manufacturing activities, review of records, and interviews with firm employees.

Quality Oversight of Framingham Specialty Care Products
(Written by Investigator Marcsisin)
The roles and responsibilities of the firm's Quality Unit are defined in the various procedures utilized by the firm. An overview of the firm's quality management system can be found on page 15 of **Exhibit 4**. For the procedure index provided by the firm, see **Exhibit 18**. The firm's Quality Unit is responsible for all Quality related activities for the manufacture and release of bulk drug substances to include deviation management, Corrective and Preventative Actions (CAPAs), Out of Specifications (OOS) investigations, and material release. Firm management also conducts Quality management review and quality council meetings for which quality indicators are reviewed. The firm's quality unit tracks and reviews trending data for deviations, CAPAs, OOS investigations, and other quality events to identify recurring issues and to appropriately address the identified issue. During the current inspection, selected quality metric trend reports were reviewed without comment.

Deviations, Investigations, CAPAs, and Change Controls
(Written by Investigator Marcsisin)
Deviations, Investigations, CAPAs, and change controls are managed in the firm's (b) (4) electronic document management system and are governed by procedures BQ-GOP-000175 – (b) (4) Change Control Processing, BQ-GOP-000249 – (b) (4) Events and CAPA Process, and BQ-GOP-000248 – (b) (4) Deviation Process. During the current inspection, the above procedures were reviewed without comment. Selected deviations, investigations, CAPAs, and change controls were selected and reviewed during the inspection (FRAD21E0968, FRAD22E0306, FRAD22E0331, 2019FRACC0071 and CAPAs initiated because of the 2017 and 2020 FDA inspections). A verbal observation was made regarding deviation FRAD22E0331 – Thyrogen-BGF4B12B-51 NYA-Chromatogram pH trend is out of specification during (b) (4) Column. See *General Discussion with Management* Section for additional information.

Annual Product Quality Reports
(Written by Investigator Marcsisin)
The firm conducts annual product quality reviews (PQR) of bulk drug substances manufactured at the Framingham site per procedure FBL-PLN-000068 – Product Quality Review Procedure for Framingham. Product quality reviews are conducted to monitor and improve product quality; identify trends, assess impact(s) of cumulative changes to validated states, and verify consistency of existing manufacturing processes. During the current inspection, the 2022 PQR for Thyrogen (FBL-RPT-001572), 2021 PQR for Cerezyme (FBL-RPT-001455), and 2022 PQR for Fabrazyme (FBL-RPT-001637) bulk drugs substances were reviewed without comment.

Biological Product Deviation Reports (BPDRs)
(Written by Investigator Marcsisin)

Initiation of biological product deviation reports (BPDRs) is governed by procedure BQ-GOP-000029 – Biological Product Deviation Reports. Since January 2017, the firm indicated that they have filed three BPDRs which are listed below:

- Firm Event ID# 60603 – 2019 OOS concentration result for Fabrazyme 4-month stability timepoint (6-10 °C), lot 9GHUP009.
- Firm Event ID# 61073 – 2019 OOS result for OOS concentration result for Fabrazyme 1-week stability timepoint (6-10 °C, expiry), lot 9GHFP002
- Firm Event ID# 63076 – 2020 OOS result for reconstitution time for 12-month stability time point (2-8°C) for Thyrogen lot 9W1648.

The above BPDRs; associated investigations, and CAPAs were reviewed during the current inspection without comment.

Control of Elemental Impurities (ICHQ3D) for Bulk Drug Substances
(Written by Investigator Marcsisin)
The firm has a risk assessment process in place to evaluate and control for elemental impurities in the Thyrogen, Fabrazyme, and Cerezyme bulk drug substances. The program is outlined by procedure BG-GOP-000294 – Elemental Impurities for Specialty Care (see **Exhibit 9**). The associated risk assessments for Thyrogen, Fabrazyme, and Cerezyme bulk drug substances can be found in **Exhibit 10**. The above information was reviewed during the current inspection without comment.

PRODUCTION SYSTEM

Cell Bank Manufacture and Storage Coverage for European Medicines Agency
(Written by Investigator Marcsisin)
The firm does not currently manufacture cell banks (master or working) at the Framingham Campus. Cell banks utilized for commercial bulk drug substance manufacture are stored in an area within building (b) (4) NYA. The firm has a back-up storage area in building (b) (4) NYA. Cell bank areas are secured; the liquid nitrogen cryogenic containers locked (keys controlled by the Quality Unit), cryogenic containers inventoried, and monitored by the firm. During the current inspection, the cell bank storage areas located at (b) (4) and (b) (4) NYA were inspected without comment.

In 2000, the firm had a former clinical manufacturing suite located at (b) (4) NYA where cell bank manufacturing activities occurred. The manufactured cell banks included the Olipudase master cell bank (MCB) lot (b) (4). The firm no longer conducts any cell bank manufacturing activities at (b) (4) NYA and has no intensions to do so in the future at the Framingham site (within any building). In 2011-2012, the (b) (4) NYA building was extensively renovated and the area where the Olipudase MCB cell bank was manufactured changed. Firm management explained that future cell bank manufacturing activities would occur at the Sanofi-Aventis Biotechnology Development site in Vitry-Sur-Seine Cedex, France. For a memorandum provided by firm management that describes the above cell banking activities, see **Exhibit 11**.

Overview of Thyrogen Bulk Drug Substance Manufacture

(Written by Investigator Marcsisin)
Thyrogen manufacture (cell culture, product purification, and BDS formulation) occurs at the firm's (b) (4) NYA building. (b) (4) NYA does not have a buffer preparation area and buffers are instead made at the (b) (4) NYA facility and transferred to (b) (4) NYA for use in Thyrogen manufacture. The firm currently has two validated Thyrogen manufacturing processes for the manufacture of the Thyrogen bulk drug substance. The firm validated an updated process that utilizes (b) (4) technology for cell culture ((b) (4)) and purification elute storage and is referred to as the (b) (4) process by the firm (b) (4) (b) (4)). For an overview of the (b) (4) process, see **Exhibit 12**. The (b) (4) manufacturing process is currently being used for Thyrogen BDS being manufactured for the U.S. market. The process flow diagram for the (b) (4) process is shown on page 3 and 4 of **Exhibit 11**. The (b) (4) process includes cell culture and expansion of the Thyrogen-CHO cell line in (b) (4)). The Thyrogen cell culture is (b) (4) ((b) (4) total, reactors (b) (4) production run. The Thyrogen manufacturing process is run in the (b) (4) mode and unpurified bulk drug substance is collected from the bioreactors at specified intervals throughout the production run. After the unpurified bulk drug substance is collected, it undergoes a (b) (4) step; (b) (4)), (b) (4), and formulation. For the validation reports for the Thyrogen BSB manufacturing process, see **Exhibits 13 – 16**. During the current inspection, the provided Thyrogen process validation reports were reviewed without comment. The second validated Thyrogen manufacturing process (process prior to (b) (4) process) utilizes (b) (4) for cell culturing activities and more open processes during purification. For an overview of the (b) (4) Thyrogen manufacturing process, see page 21 of **Exhibit 3 and Exhibit 17**. Firm management indicated that the (b) (4) manufacturing process is no longer being utilized to manufacture BDS for the U.S. market and that the last (b) (4) BDS lot for the U.S. market was manufactured in April 2022 (pooled formulated bulk BDS lot CGFPS003).

Observation of Thyrogen Bulk Drug Substance Manufacture
(Written by Investigator Marcsisin)
During the current inspection, the following Thyrogen manufacturing activities were observed without comment:

- On 7/18/2022, cell culture and environmental monitoring activities in room (b) (4) for (b) (4) (b) (4), lot CGFFSS009).
- On 7/18/2022, overview of how the 130 mL harvest for lot CGF2B08 was collected from (b) (4) production bioreactor in room (b) (4).
- On 7/19/2022, Thyrogen elution from the (b) (4) chromatography step for lot CGF1B03A.

Production Record Review
(Written by Investigator Marcsisin)
During the current inspection, selected Thyrogen inoculum and purification manufacturing records were reviewed (to include lot 8GFSB04V) without comment.

(b) (4) Testing of Thyrogen Process (b) (4)

(Written by Investigator Marcsisin)
The Thyrogen manufacturing process requires multiple (b) (4) steps during BDS purification as shown on page 4 of **Exhibit 12 and Exhibit 17**. Additionally, the firm utilizes various process (b) (4) to include (b) (4) during bioreactor operations. The various (b) (4) utilized by the firm are tested for integrity (b) (4)) and the type of test conducted (i.e., (b) (4)) is dependent on the (b) (4) type. The firm utilizes electronic (b) (4) testers for (b) (4) of process (b) (4). During the current inspection, the (b) (4) tester located in room (b) (4) was inspected and the electronic results log audited. It was noted during review of the electronic log that the firm is not auditing the electronic records of the testers and that not all (b) (4) test data are being incorporated into the firm's logbooks as required per procedure. See **Observation 1**for additional information.

FACILITIES AND EQUIPTMENT SYSTEM
Overview of the Firm's Framingham Campus
(Written by Investigator Marcsisin)
The firm's Framingham site is a multibuilding campus as shown on page 9 of **Exhibit 3**. The firm has buildings for Thyrogen BDS manufacture (b) (4) NYA), biosurgery and sodium hyaluronate manufacture (b) (4) NYA), Thyrogen buffer preparation/QC laboratory/cell bank storage (b) (4) NYA), COVID-19 vaccine manufacturing/back-up cell bank storage (b) (4) NYA), 2nd generation Fabrazyme BDS and integrated continuous bioprocessing of Cerezyme and Fabrazyme BDS (b) (4) NYA) and administrative support/QC laboratory (b) (4) NYA). All buildings on the campus are secured and employee access is granted through ID badge access. Operations within buildings (b) (4) NYA, (b) (4) NYA, (b) (4) NYA, (b) (4) NYA, and (b) (4) NYA were covered during the current inspection. Building (b) (4) NYA is the building where Thyrogen BDS is manufactured and was the current focus of the current inspection. (b) (4) NYA is an approximately (b) (4) square foot facility with areas for receiving/loading dock, cold storage, offices, gowning, equipment storage/cleaning, (b) (4) (b) (4) . For a facility diagram of building (b) (4) NYA, see **Exhibit 19**. The rooms/areas within building (b) (4) NYA have different classifications (grades A, C, D & controlled non-classified) depending on the nature of manufacturing activities conducted in the area. During the current inspection, the various areas of building (b) (4) NYA were inspected, and deficiencies noted. See **Observation 2** for additional information. Per firm management, (b) (4) NYA's next planned shutdown is in (b) (4) . The firm intends on conducting facility preventative and corrective maintenance and to replace (b) (4) HVAC units during the (b) (4) shutdown. For a list of work items to be completed during the shutdown, see **Exhibit 27**.

Cleaning Validation and System Suitability Measurements for Thyrogen (b) (4) Manufacturing Steps
(Written by Investigator Marcsisin)
The firm conducts (b) (4) steps during the Thyrogen BDS manufacturing process. During the current inspection, I reviewed the firm's cleaning process validation report (study# 02-1043) for the (b) (4) system without comment. I reviewed system suitability measurements (normalized permeability) for a selected (b) (4) membrane without comment.

Environmental Monitoring Program and Trending
(Written by Investigator Marcsisin)
The firm has an environmental monitoring (EM) program for building (b) (4) NYA is governed by procedures FBL-SOP-000826 – Environmental Monitoring of the (b) (4) NYA Manufacturing Area (**Exhibit 20**), FBL-SOP-000189 – Monitoring the Critical Utility Systems at the (b) (4) New York Avenue Facility, and FBL-SOP-001222 – Environmental Monitoring, Water, Steam, and Gas Systems (b) (4) Trending for the Framingham Campus. Within building (b) (4) NYA, the firm conducts EM of grade-A areas during each use, (b) (4) monitoring of grade-C areas, and (b) (4) monitoring of grade-D areas and carts. EM of manufacturing areas consists of active air-viable, surface viable, and non-viable particulate monitoring. During the current inspection, I reviewed the (b) (4) NYA manufacturing (b) (4) trend reports (FBL-RPT-0011664 & FBL-RPT-001592) without comment. Additionally, I reviewed the (b) (4) NYA critical utilities (b) (4) trend reports (FBL-RPT-001586 & FBL-RPT-001658) without comment.

Equipment Alarm Systems
(Written by Investigator Zheng)
The firm uses the automation software (b) (4) to monitor and operate production equipment, including bioreactors (b) (4) used for production of Thyrogen and located in Room (b) (4) at the (b) (4) NYA site. (b) (4) can communicate with operators through alarms, prompts, and messages. Prompts are associated with control of production steps and require operator acknowledgement to proceed. Operators are trained to acknowledge prompts on the (b) (4) human-machine interface (HMI) and document the step in the batch record.

Messages indicate circumstances related to the (b) (4) software and/or servers. Per vendor documentation, messages are unable to affect production conditions. Operators are trained to acknowledge messages without being required to document the event.

Additionally, (b) (4) triggers Warning, Critical, and Quality Critical alarms in response to parameter failures during the production cycle. Operators are trained to acknowledge and respond to alarms, including documenting the alarm in the batch record and in (b) (4), an event-capture software that the firm uses for QC. Supervisors are responsible for verifying proper acknowledgement of alarms contemporaneously as well as for reviewing the batch record against the (b) (4) alarm history for accuracy. An alarm triggers an audible noise as well as emails and phone calls to area management. During this on-site inspection, I reviewed the (b) (4) alarm history on bioreactor (b) (4), which included a Critical alarm for an aborted (b) (4) cycle, a Warning alarm for pH out of specification, and a Quality Critical alarm for pH out of specification. I reviewed the firm's documentation of and response to the (b) (4) alarms without comment.

On 7/18/2022, during a walkthrough of the facility, I noted the presence of an error message on multiple (b) (4) HMIs reading "Error – 2147212502 8004232a Network Transaction is in progress." The firm explained that (b) (4) error messages are from the (b) (4) server rather than the production equipment. The firm also provided vendor documentation showing that (b) (4) errors are unable to

affect the production process (see **Exhibit 47**). Operators are not required to record (b) (4) error messages in the batch record.

Room Use and Cleaning Logs

(Written by Investigator Zheng)

The firm uses manufacturing execution software (b) (4) to manage production records and document room use and cleaning. (b) (4) records room status as (b) (4) and enforces certain limitations such as automatically changing status from (b) (4) at the conclusion of production activities and prohibiting operators from changing room status from (b) (4) (b) (4). The firm also maintains paper logbooks to document room cleaning, which are maintained by cleaning supervisors and secured by the firm's Records department. Operators are responsible for logging room status as (b) (4) in (b) (4) prior to production activities.

During the walkthrough of the (b) (4) facility, I noted (b) (4) paper room use logbooks: 2022LBF0013 for Room 152, 2022LBF0014 for Room 152A, 2022LBF0096 for Room 152B, and 2022LBF0095 for Room 153. While reviewing the logbooks, I pointed out to the firm that in all (b) (4) logbooks, entries dating from Feb. 10, 2022 to Jul. 16, 2022 were not reviewed until Jul. 17, 2022. According to Greg Klotz, Manager of Manufacturing Specialist, the firm had identified this issue and opened an investigation on Jun. 29, 2022. During this on-site inspection, the investigation determined per (b) (6), Senior Quality Engineer that these particular logbooks should have been obsoleted when the firm transitioned from paper room use logbooks to (b) (4) in 2017. The firm has initiated a CAPA to obsolete the logbooks and modify written procedures accordingly, which I reviewed without comment.

Laminar Flow Hoods

(Written by Investigator Zheng)

Recertification of HEPA filters in the firm's hoods is governed by FBL-SOP-000698 Certification of HEPA Filters (see **Exhibit 48**). According to (b) (6), Metrology Operations Support Group Lead, HEPA filters in LFHs rated and monitored to Grade A are recertified (b) (4). Per the procedure, recertification involves testing (b) (4) (b) (4). According to the firm, damage, staining, or recertification failure would lead to HEPA replacement. During this on-site inspection, I reviewed all HEPA filter recertifications from 2020-2022 for LFHs FB-2074 and FB-16384. I noted that, for all filter integrity tests on these two hoods between 2020-2022, the upstream concentration setting failed to meet recommended parameters in the procedure. For example, FBL-SOP-000698 states that, for filter integrity testing using a (b) (4) (b) (4) should be between (b) (4) (see page 15 of **Exhibit 48**). The Certification Datasheet for recertification of FB-2074 on Mar. 22, 2022 indicates that the upstream concentration was set to 18 ug/L. While discussing with the firm, (b) (6) agreed that the procedures were outdated and explained that the recommended concentration settings were a holdover from Sanofi's Allston location which no longer exists. The firm indicated that procedures would be updated to be in line with current practice. Additionally, Mr. Dodakian noted that FBL-SOP-000698 establishes an acceptable range on the (b) (4) of (b) (4) which I accepted without comment.

Cleaning and disinfecting of the firm's hoods are governed by FBL-SOP-000692 Use of Laminar Flow Hoods, Biological Safety Cabinets, and Fume Hoods. According to the procedure, hoods receive routine cleaning with (b) (4) on a (b) (4) schedule and between products or after a major spill, with a contact time of (b) (4) . Hoods also receive disinfection with (b) (4) at (b) (4) (b) (4) when not in use, with a contact time of (b) (4) , as well as with (b) (4) (b) (4) before each use, at the end of a production day, or after a minor spill, with a contact time of (b) (4) Following contact time, operators wipe all surfaces using saturated (b) (4) wipes, specifically (b) (4) , to remove cleaning solution residue. During the inspection, I requested and the firm provided vendor technical information for the (b) (4) . While reviewing documentation, I pointed out to the firm that the manufacturer does not recommend use of (b) (4) in Grade A environments, such as in FB-2074, FB-16384, and other production hoods monitored and rated as Grade A. The firm agreed that the wipes were being used outside manufacturer recommendations but justified their use by noting that the firm's environmental monitoring parameters in the hoods exceeded Grade A requirements.

LABORATORY SYSTEM

Overview of the Firm's QC Laboratory

(Written by Investigator Marcsisin)

The firm has several QC laboratory areas at the Framingham site which are located at (b) (4) NYA and (b) (4) NYA. The (b) (4) NYA QC laboratory was inspected during the current inspection. The QC laboratory located at (b) (4) NYA has multiple high pressure liquid chromatography (HPLC) instruments for the various tests conducted by HPLC. The laboratory has cold storage areas for sample storage and other pieces of laboratory equipment. The QC laboratory at (b) (4) NYA was inspected without comment.

Out of Specification (OOS) Investigations

(Written by Investigator Marcsisin)

Investigations into out of specification results is governed by procedure BQ-GOP-000245 – (b) (4) (b) (4) . Investigations are documented and tracked through the firm's (b) (4) electronic system. Laboratory investigations consist of several phases which include an initial investigation to determine if a laboratory error occurred. If a laboratory error is not found, then the investigation continues (b) (4) and includes an expanded laboratory investigation. During the current inspection, selected ILI investigations (FRAD22L00021, FRAD21L00045, FRAD21E0498) were requested and reviewed without comment.

Thyrogen Stability Program

(Written by Investigator Marcsisin)

The firm has a stability program for the Thyrogen BDSs manufactured at the Framingham site. The stability studies are overseen by the firm's stability group and stability analyses are conducted in the firm's QC laboratory in (b) (4) NYA. Stability studies are governed by stability protocols that outline required stability storage conditions, tests, and timepoints. During the current inspection, the documentation for the Thyrogen BDS 24-month stability sample (stored at (b) (4) for lot 8GF4B3V was reviewed without comment. Additionally, bioassay data and the electronic source chromatography data for the aggregation test were reviewed without comment for the above sample.

MANUFACTURING CODES
(Written by Investigator Marcsisin)
The firm assigns unique identifiable lot codes to BDS intermediates and formulated BDSs as per procedure FBL-SOP-000953 – Lot Numbering System.

COMPLAINTS
(Written by Investigator Marcsisin)
The firm's complaint handling process is governed by procedure FBL-SOP-000056 – Product Event Investigation for Material Manufactured in Framingham Biologics. The firm's global event management group is responsible for the intake of complaints related to drug products and an investigation is initiated in the (b) (4) complaint management system. A sub-investigation is assigned to Framingham Biologics if a review/assessment of the BDS manufacturing process for the affected product is needed. During the current inspection, I reviewed the following (b) (4) complaint and sub-complaint investigations without comment:

- (b) (4) Complaint ID: 100130697 – 2021 Complaint for particles observed in reconstituted Fabrazyme (finished drug product). Sub-investigation 300065098. Determined to likely be protein (Fabrazyme) flocculation.
- (b) (4) Complaint ID: 100055003 – 2022 Complaint for foreign matter observed in reconstituted Fabrazyme (finished drug product). Sub-investigation 300024772.
- (b) (4) Complaint ID: 100227599 – 2022 Complaint for foreign matter observed in reconstituted Fabrazyme (finished drug product). Sub-investigation 300103127.

RECALL PROCEDURES
(Written by Investigator Marcsisin)
The firm's recall process is governed by procedures GOP-000165 – Management of Recalls, and FBL-SOP-001019 – Recall Management for Framingham Biologics and Biosurgery Sites. The firm conducts (b) (4) mock recalls. Firm management stated that no BDS recalls have occurred since the 2017 FDA inspection.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

OBSERVATION 1
Failure to exercise sufficient controls over computerized systems and failure to have adequate controls to prevent omission of data.

Specifically,

The firm utilizes (b) (4) testers (b) (4) total testers) for (b) (4) testing of cell culture and purification process filters during Thyrogen (Thyrotropin alfa) bulk drug substance manufacture. An audit trail review assessment as required per procedure BQ-GOP-000300 "A Risk Based Approach to Audit Trail Review (ATR) for Computerized Systems" – version 3.0, effective date 04/07/2022, has not been performed for the (b) (4) testers utilized for critical GxP decision points during Thyrogen bulk drug substance manufacture. Additionally, no

review of the electronic logs/audit trails of the (b) (4) testers was performed to ensure all GxP data are reviewed and incorporated into the firm's manufacturing records and MES logbooks. For example, on 6/9/2022, the firm (b) (4) tested the clarification process (b) (4) 1041-05, SFO-1378345), which was documented as passing specification in the firm's logbook. On 7/19/2022, we reviewed the (b) (4) tester (tester# 3000242) electronic results log and noted three additional tests for the (b) (4) which included two failed tests and a canceled test by an operator (as evidenced by code ID: 9175). The two failed and cancelled tests were not recorded in the firm's MES logbook, and no documentation was made as to why the test was cancelled. Since January 2022, the firm has manufactured (b) (4) lots of Thyrogen bulk drug substance utilizing data from the (b) (4) testers without adequately reviewing the electronic logs/audit trails of the testers.

Supporting Evidence, Relevance and Discussion with Firm Management
(Written by Investigator Marcsisin)
During the current inspection, Investigator Zheng and I inspected the firm's Thyrogen manufacturing areas to include room (b) (4). Room (b) (4) is utilized by the firm for production scale bioreactor operations during Thyrogen manufacture. Room (b) (4) also contains additional equipment to include a (b) (4) skid and (b) (4) tester (tester# 3000242) for (b) (4) testing (b) (4). Per firm management, the firm has (b) (4) testers. For a list of Thyrogen BDS lots manufactured using data from the (b) (4) testers since January 2020, see **Exhibit 28**. For a photograph of the (b) (4) tester (tester# 3000242), see page 1 of **Exhibit 22**. Page 4 of **Exhibit 12 and Exhibit 17** show that there are multiple (b) (4) steps during Thyrogen manufacture (as indicated by the (b) (4) (b) (4)). I asked the firm to show me the electronic results log of the (b) (4) (b) (4) tester. The screen displaying this function is shown on page 1 of **Exhibit 22** as the F1 function – Test results from internal memory. Firm management explained that an administrator would have to create a modified account so that the function could be accessed. On 7/20/2022, I spoke with Tara Girshick – Director, QA Digital, and (b) (6) – Analytical Systems Engineer, regarding the (b) (4) tester (tester# 3000242). (b) (6) is the system administrator and logged in and created an account so that the electronic results log could be viewed. When the electronic results log was opened by (b) (6), the previous (b) (4) tests performed on the tester were viewable as shown on pages 2 – 5. The information displayed on the electronic results log for the tester included the test number "No.", test date "Date", "Serial no.", test type "Type", "Name" and result column "Res". The results column on page 4 of **Exhibit 22** show that the results logged can be pass (indicated by (b) (4)), fail (indicated by (b) (4)), and a no result (can be due to cancelled test, indicated by (b) (4). I noted several tests for which there were multiple failed (b) (4) tests along with cancelled tests to include test numbers 41-45 (conducted on 6/30/2022-7/1/2022, see page 5 of **Exhibit 22**), and test numbers 72-74 (conducted on 6/9/2022, see page 2 and 3 of **Exhibit 22**). From the results log, a specific test could be selected by (b) (6) and the test results printed. I had (b) (6) print the test results for the above specified tests on the specified test dates and the results shown in **Exhibit 23**. The results on page 1 of **Exhibit 23** are for (b) (4) 4972-01 (b) (4) utilized for bioreactor operations), shop floor order (SFO#1390916) tested on 6/30/2022-7/1/2022 and the results on page 2 of **Exhibit 23** are for (b) (4) 1041-05 (b) (4), utilized for clarification of BDS), shop

floor order (SFO#1378345) tested on 6/9/2022. See page 57 and 59 of **Exhibit 24** for descriptions of the above (b) (4) and the type of (b) (4) est required. **Exhibit 25** shows the required use of (b) (4) 1041-05 (b) (4) filter) during the clarification and concentration operation for the Thyrogen BDS (lot 8GF2B01VC). While reviewing the results from 6/9/2022 for (b) (4) 1041-05 (SFO#1378345), I noted a failed test conducted at 13:03, a cancelled test conducted at 13:15 (as indicated by the note on the printout and ID: 9175), a failed test conducted at 13:16, and a passing test for the (b) (4) conducted at 13:53. I inquired as to why the test at 13:15 was cancelled and if operators can cancel tests. (b) (6) – Senior Manufacturing Associate, logged into the (b) (4) tester and showed me his ability to cancel a test and receive the ID: 9175 message. (b) (6) only has operator privileges for the tester, not administrator privileges. The firm's procedure for the use of the (b) (4) tester is shown in **Exhibit 24**. Per section 6.7.2.8 of **Exhibit 24** (page 41), (b) (4) (b) (4) (b) (4) ." Per section 6.7.2.7 of **Exhibit 24** (page 40), (b) (4) (b) (4) initiate a deviation per BG-GOP-000248." Additionally, operators are to document all records generated during (b) (4) testing in the firm's MES (manufacturing execution system) logbook as per sections 6.5.1.1 & 6.5.1.2 (page 34 of **Exhibit 24**).

On 7/21/2022, I spoke with Christopher Holmes – Associate Director of Manufacturing – Cell Culture, and Jacob Kallon – Senior Manager of Purification, about the (b) (4) test results for (b) (4) 4972-01 (SFO#1390916) and 1041-05 (SFO#1378345). I inquired as to why tests for the two (b) (4) had been cancelled. Mr. Kallon and Mr. Homes explained that the test for (b) (4) 4972-01 (SFO#1390916) was canceled because the operator did not properly (b) (4) and that the test for (b) (4) 1041-05 (SFO#1378345) was canceled because the operator heard a "hissing" sound. I asked Mr. Kallon and Mr. Holmes if the canceled tests were captured in the MES logbook. Mr. Holmes stated that they were not. I asked Mr. Kallon and Mr. Holmes if they were aware of the canceled tests prior to me bringing them to the firm's attention. Mr. Kallon and Mr. Holmes both stated that they were not aware of the canceled tests.

On 7/25/2022, I asked firm management for the MES logbook pages that showed the various tests described above for (b) (4) 1041-05 (SFO#1378345). The firm provided a single result in the MES logbook as shown in **Exhibit 26**, which only documented the passing (b) (4) test conducted at 13:53 on 6/9/2022. I inquired as to if the other tests conducted for (b) (4) 1041-05 (SFO#1378345), were documented in the MES logbook. Mr. Kallon explained that the other results (2 failing tests, 1 canceled test), were not documented in the MES logbook. I asked Mr. Kallon as to why they results were not documented. Mr. Kallon explained that he spoke with the operator and that the operator explained that they did not know that they were supposed to attach all printouts from the (b) (4) tester to the MES logbook.

On 7/21/2022, I spoke with Tara Girshick – Director QA Digital, regarding the (b) (4) (b) (4) testers. Ms. Girshick explained that the (b) (4) testers were older systems and considered legacy electronic systems by the firm. Ms. Girshick showed me the firm's procedure regarding audit trail review of computerized systems - SOP BQ-GOP-000300 - A risk based approach to audit trail

review for computerized systems (see **Exhibit 29** for the firm's current version). See **Exhibit 30** for the previous version of the procedure. Ms. Girshick explained for computerized systems, that the firm conducts assessments of computerized system audit trail review via SOP BQ-GOP-000300 utilizing an assessment Form BQ-FRM-000899 (**Exhibit 31**). Ms. Girshick pointed to page 2 of **Exhibit 31** and showed me the risk matrix for determining how often audit trail review is required. For systems that generate data for GxP decision support (e.g., (b) (4) testing data), the firm is required to audit the computerized system (b) (4) . I inquired if such an assessment had ever been conducted for the (b) (4) testers. Ms. Girshick explained that since the (b) (4) testers were electronic equipment systems, that she was not sure they would be defined as computerized systems and might not be within scope of the procedure. Ms. Girshick explained that she would have to look into the firm's definition of a computerized system. Ms. Girshick explained that she thought that the electronic equipment would likely be considered a sub-system of a computerized system and therefore a gap likely existed in the firm's procedure for audit trail review of electronic systems. Ms. Girshick explained that the (b) (4) testers did have a data integrity assessment conducted. Firm management provided the noted data integrity assessment (see **Exhibit 32**).

On 7/22/2022, I spoke with Ms. Girshick again about the (b) (4) testers. Ms. Girshick provided procedure FBL-SOP-000635 – GxP Evaluation and Electronic Records and Electronic Signatures (ERES) Assessment Procedure (**Exhibit 33**). Ms. Girshick pointed out that per page 14 and 15 of **Exhibit 33**, that electronic equipment are defined as a sub-system of computerized equipment. Ms. Girshick explained that the firm had misclassified electronic equipment (i.e., (b) (4) testers), and is why the (b) (4) testers were not evaluated per SOP BQ-GOP-000300 and Form BQ-FRM-000899 (**Exhibits 30 & 31**).

On 7/25/2022, I spoke with Ms. Girshick again about the (b) (4) testers. Ms. Girshick explained that it appeared that the (b) (4) testers should have been assessed per SOP BQ-GOP-000300 and Form BQ-FRM-000899. Ms. Girshick stated that the firm would have to workout how to do audit trail assessments moving forward and that they would likely have to be geared/directed towards the type of data generated by the equipment. Ms. Girshick stated that the deviation opened by the firm for the observation (FRAD22E0608, **Exhibit 34**), would likely have to be explained in scope to include impacted equipment during the investigation.

On 7/25/2022, I reviewed the observation with firm management during the inspection closeout meeting. Mr. Yudiski stated that the firm planned on responding to the observation.

OBSERVATION 2
Failure to properly maintain buildings and facilities used in the manufacture of bulk drug substances.

Specifically,

The firm does not properly maintain building (b) (4) which is utilized for Thyrogen bulk drug substance manufacture. During the current inspection, the following items were noted:
• On 7/18/2022, we noted what appeared to be rust on the interior of the sash handle within the grade-A area for biological safety cabinet (BSC# FB-2074 in room (b) (4) . The firm was able to wipe

and dislodge the material that appeared to be rust within the grade-A area. Room (b) (4) (grade-C room) is the firm's (b) (4) area and is utilized for the final manufacturing steps of Thyrogen bulk drug substance. What appeared to be rust was also noted on the exterior of the hood and on ceiling grates in room (b) (4). Thyrogen bulk drug substance lot CGFPS003 was manufactured in room (b) (4) utilizing BSC# FB-2074 in April 2022.

• On 7/18/2022, we noted that the floors within grade-C rooms (b) (4) were chipped in multiple areas throughout the rooms. Rooms (b) (4) are utilized for small scale cell culture manufacturing activities for Thyrogen bulk drug substance.

• On 7/20/2022, we observed a puddle of unidentified standing liquid in the grade-D room (b) (4) located underneath and behind the (b) (4) skid, while the room was in use for production of commercial Thyrogen product (lot CGF2B08). We also observed cracks in the floor adjacent to the noted puddle.

• On 7/19/2022, we observed what appeared to be a leak from a (b) (4) lock fitting for Reactor D1 which puddled on the floor in grade-D Room (b) (4) while the room was in use for production of commercial Thyrogen product.

• On 7/22/2022, we observed what appeared to be a leak from (b) (4) (#AE-971003) for the firm's (b) (4) The firm's (b) (4) water system is utilized for Thyrogen bulk drug substance manufacturing activities and to feed the firm's water for injection generation system in building (b) (4)

Supporting Evidence, Relevance and Discussion with Firm Management
(Written by Investigator Marcsisin)
It should be noted that the 3rd and 4th bullet points of the Form FDA 483 for this observation were amended during the current inspection to correct the room number from 190 to 140. See below and **Attachment 3**.

Observation 2 - 1st bullet point
(Written by Investigator Marcsisin)
On 7/18/2022, Investigator Zheng and I inspected room (b) (4). Room (b) (4) is utilized by the firm to further process (b) (4) Thyrogen BDS and is considered the (b) (4) side of the Thyrogen purification process. For a process flow diagram, see page 4 of **Exhibit 12**. Within room (b) (4) there is a biological safety cabinet (BSC# FB-2074) utilized for handling/manipulation of (b) (4) Thyrogen BDS. Page 3 of **Exhibit 36** shows that the firm utilized BSC# FB-2074 during the manufacture of Thyrogen BDS intermediate lot CGFP003 (see page 1of **Exhibit 36**). Thyrogen BDS intermediate lot BGF1S11was then utilized for the Thyrogen BDS formulated lot CGFPS002. The interior of the BSC is classified as grade-A by the firm (see page 36 of **Exhibit 20** which lists the BSC# FB-2074 as a grade-A environment). Upon inspection of the interior of the BSC on the sash handle, I noted unknown brown grime and material that appeared to be rust. See page 15-17 of **Exhibit 21**. I also noted what appeared to be rust on the bottom air vent in front of the BSC (see page 20 of **Exhibit 21**) and what appeared to be rust on the exterior hood surface and on the ceiling grates within room (b) (4) (see pages 18-19, 21-22 of **Exhibit 21** respectively). For the unknown brown

material noted within the grade-A area in BSC# FB-2074, the firm was able to wipe the material off with a sterile wipe. See **Exhibit 35** of the wipe that the firm showed Investigator Zheng and I after wiping the noted area within BSC# FB-2074.

On 7/19/2022, I spoke with Maggie Snow – Director Quality Compliance, and Gary Dodakian – Head of Quality Framingham Biologics, regarding the unknown brown material wiped from BSC# FB-2074. I showed Ms. Snow and Mr. Dodakian the wipe and asked if the material had come from within the grade-A area. Ms. Snow and Mr. Dodakian acknowledged that it had come from the grade-A area. I asked the firm if they expected the material to be within the grade-A area. Both Ms. Snow and Mr. Dodakian explained that they did not expect the material to be in the grade-A area.

On 7/21/2022, I spoke with Nick Shoenfelt – Senior Manager of Support Services, Brandon Scandlon – Associate Director of Contamination Control, and Joseph Panella – Senior Director Manufacturing, regarding the firm's facility maintenance program and facility walkthrough program. Firm management explained that they have walkthrough programs in place to evaluate for facility issues as outlined in procedures SOP FBL-SOP-000709 - Walk-through procedure for Framingham Biologics (**Exhibit 37**) and SOP BG-BOP-000260 - Walk-through inspections (**Exhibit 38**). I requested the (b) (4) walkthrough documentation for the firm's bioreactor room (b) (4) cell culture area, and downstream purification area (to include room (b) (4)). Firm management provided the requested walkthrough documents from May 2022 (cell culture and downstream purification areas, **Exhibit's 40 & 41**) and June 2022 (Environmental Action Committee walkthrough, bioreactor room, **Exhibit 39**) and I noted that the unknown brown material in BSC# FB-2074 was not documented in May 2022 walkthrough (see **Exhibit 41**). Additionally, per page 19 of the firm's procedure - SOP FBL-SOP-000709 - Walk-through procedure for Framingham Biologics (**Exhibit 37**): "Rooms with Biosafety Cabinets must include a visual inspection of the BSC for general wear and tear on the unit, such as the formation of rust and chipping paint".

On 7/22/2022, firm management provided pictures of the remediation of BSC# FB-2074 (see pages 15 and 16 of **Exhibit 44**. On 7/25/2022, during the inspection closeout meeting, I reviewed the observation with firm management. Mr. Yudiski stated that the firm planned on responding to the observation.

Observation 2 – 2nd bullet point
(Written by Investigator Marcsisin)
On 7/18/2022, Investigator Zheng and I inspected the firm's cell culture areas and I noted that the floors within grade-C rooms (b) (4) were chipped in multiple areas throughout the rooms. See pages 3-11 of **Exhibit 21**. Rooms (b) (4) are utilized for small scale cell culture manufacturing activities for Thyrogen bulk drug substance. The May 2022 (b) (4) facility walkthrough document is shown in **Exhibit 40** and no observations regarding the floor are documented. On 7/22/2022, I inquired about the chipped floors with firm management. Firm management explained that the floors would be repaired during the October 2022 facility shutdown of building (b) (4) NYA. On 7/25/2022, during the inspection closeout meeting, I reviewed the observation with firm management. Mr. Yudiski stated that the firm planned on responding to the observation.

Observation 2 – 3rd bullet point
(Written by Investigator Zheng)
On 7/20/2022, during a walkthrough of Room (b) (4) in (b) (4) NYA, I observed a puddle of unidentified standing liquid located behind the (b) (4) skid while the room was in use for production of Thyrogen lot CGF2B08. The puddle was situated in a low point in the floor immediately adjacent to a raised section preventing drainage (as documented in **Exhibit 44** as request ID 111). I also observed cracks in the floor nearby which appeared to be due to water damage (see pages 12 & 13 **Exhibit 21**). During this on-site inspection, the firm determined that the puddle consisted of water that had splashed out during (b) (4) water sampling from a port located immediately behind the (b) (4) skid. The firm agreed with our concerns regarding the presence of standing liquid in the production room, and Mr. Dodakian indicated the firm planned to re-slope the floor to remediate the issue.

Observation 2 – 4th bullet point
(Written by Investigator Zheng)
On 7/19/2022, during a walkthrough of Room (b) (4) in (b) (4) NYA, I observed an unidentified liquid dripping from a pipe on bioreactor D1 and puddling on the floor while the room was in use for commercial Thyrogen product (as documented on page 1 of **Exhibit 44** as request ID 177, and also via the workorder shown on page 2 & 3). During this on-site inspection, the firm determined that a (b) (4) had loosened in a manner that could not be tightened, causing some post-process water to leak out. The firm agreed with our concerns regarding leaking equipment and the presence of standing liquid in the production room and initiated a work order to remediate the issue.

Observation 2 – 5th bullet point
(Written by Investigator Marcsisin)
On 7/22/2022, Investigator Zheng and I inspected the process utilities for (b) (4) NYA. The firm's (b) (4) system is utilized throughout the facility as well as serving as a feed stream for the (b) (4) generation system. During inspection of the firm's (b) (4) system, I noted a puddle underneath the (b) (4) system and what appeared to be a leaking pH probe (probe AE-971003, see pages 30-32 of **Exhibit 21**). During the inspection, firm management provided the planned activities for the October 2022 planned shutdown of (b) (4) NYA (**Exhibit 27**). Per page 5 of **Exhibit 27**, the firm is planning on fixing the leaking probe via work order 2895207. On 7/25/2022, during the inspection closeout meeting, I reviewed the observation with firm management. Mr. Yudiski stated that the firm planned on responding to the observation.

REFUSALS
(Written by Investigator Marcsisin)
No refusals were encountered.

GENERAL DISCUSSION WITH MANAGEMENT
Summary discussions addressing cGMP issues were held at the end of inspection days to ensure the firm was aware of our findings. On 7/25/2022, we met with the management team for a closeout discussion. We then issued the 2-item FDA-483, Inspectional Observations (**Attachment 2**) to Larry Yudiski – Head of 8 New York Ave. Manufacturing and Interim Site Head. I described the 15-

business day time-frame for voluntary responses to each Observation to the agency and also provided the firm with the Pharm-1 division handout with instructions on sending 483 responses electronically (to the ORAPHARM1_RESPONSES@FDA.HHS.GOV email). I explained each observation and asked if there were any questions/comments and/or a response after each observation. For each observation, firm management stated they planned on responding to the observation. After issuance of the initial Form FDA 483, Mr. Dodakian pointed out that the room listed in **Observation 2, 3rd and 4th bullet points** (room (b) (4), should read room (b) (4) (Thyrogen production bioreactor room). I acknowledged Mr. Dodakian's correction and re-issued an amended Form FDA 483 (**Attachment 3**) to Mr. Yudiski. Firm management had no other comments.

Additionally, the following items were discussed with firm management during the inspection, however, not included on the Form FDA 483:

1. During review of Deviation FRAD22E0331 for an OOS pH measurement during a column rinse step (result below specification of pH (b) (4) I noted that the firm standardizes the chromatography pH probes using calibrant solutions of pH 4, 7, and 10 (see **Exhibit 42**). I noted to firm management that while the OOS measurement noted in Deviation FRAD22E0331 was for a rinse step not related to a specific product purification step, that the firm still had a pH measurement specification and that the value was OOS. I also noted that the firm was making measurements outside the standardization bracket of pH 4,7,10 and that the standardization bracket should encompass all pH measurements made. Firm management acknowledged my concern.

2. On 7/18/2022, Investigator Zheng and I inspected (b) (4) NYA and noted what appeared to be rust on wash racks and equipment (see page 1 of **Exhibit 21**). I noted to firm management that surface non-uniformities should be identified and assessed whenever they are observed, not just between occurrences of preventative maintenance. Firm management acknowledged my concern.

3. During inspection of (b) (4) NYA, Investigator Zheng and I noted in-process manufacturing retain samples from December 2021 in the firm's cold storage area (room (b) (4). Firm management later provided deviation FRAD22E0607 (**Exhibit 43**) for the observation as the retain samples are to be transferred to QC with (b) (4) hours and certain samples frozen (e.g., rhTHS mycoplasma retain).

4. During inspection of the Thyrogen buffer preparation area for (b) (4) NYA, I noted clean equipment being stored on carts with an unknown white crusty residue (see page 27-29 of **Exhibit 21** for photographs). I noted that clean equipment should not be stored on surfaces that appear unclean due to the potential risk of cross contamination. Firm management acknowledged my observation and explained that the bottom platform had been replaced by a wire rack after the observation and that the unknown white crusty residue did not appear to come off the cart surface. Firm management acknowledged my observation.

5. During inspection of the Thyrogen buffer preparation area for (b) (4) NYA, I noted unknown residue on the exterior of "clean" buffer preparation tanks V-1501 and V-1502 (see pages 23-26 of **Exhibit 21** for photographs). Firm management acknowledged my observation.

ADDITIONAL INFORMATION
(Written by Investigator Marcsisin)
Photographs taken during the inspection were burned onto a CD and placed into a sealed Form FDA 525 (see **Exhibit 1**) and included with the hard copy inspectional exhibits. Electronic records provided by the firm on a USB flash drive were placed in a sealed FDA Form 525 (see **Exhibit 2**) and included with the hard copy inspectional exhibits. Working copies of the photographs and electronic records collected during the inspection were placed on CD's and included with the physical exhibits of the inspection.

SAMPLES COLLECTED
(Written by Investigator Marcsisin)
No samples were collected during the current inspection.

VOLUNTARY CORRECTIONS
(Written by Investigator Marcsisin)
During the current inspection, firm management provided evidence of corrective action implementation and/or initiation as a result of selected observations made during the inspection. The provided corrective actions can be found in **Exhibit 44**.

During the current inspection, firm management provided evidence of corrective actions to the 2017 FDA inspection discussion items/verbal observations (see **Exhibit 45**). The corrective actions were reviewed without comment.

During the current inspection, firm management provided evidence of corrective actions to the 2020 FDA inspectional observations and discussion items/verbal observations (see **Exhibit 46**). The 2020 Form FDA 483 observations are specific for operations at (b) NYA. For the Form FDA 483 observations, the firm completed the following corrective actions:

Observation 1 – Facilities and equipment supporting manufacture are not adequately maintained.

Corrective Actions for 1A
The firm initiated a workorder to remove the residual (b) (4) /residue and updated procedures FBL-SOP-000093, FBL-EWI-000017, and FBL-EWI-000005 to prevent the re-occurrence.

Corrective Actions for 1B
The firm corrected the incorrectly installed HEPA pre-filter and reviewed prior differential pressure data to ensure the system was operating within operational ranges. The firm also updated the area walkthrough job plan for inspection of fit and finish including to ensure proper pre-filter installation.

Corrective Actions for 1C

The firm corrected the unsecured air supply diffusers within the controlled non-classified space. The firm also updated the associated job plan for inspection to ensure air supply diffusers are secured properly.

Observation 2 – Equipment used within the QC Microbiology Laboratory has not been certified and review of logbooks had not been conducted according to procedure.

Corrective Actions for 2A
The firm reviewed (b) (4) balances in service and found only one had not undergone (b) (4) certification. The firm opened deviation FRAD20E0760; determined the root cause and updated associated documents to prevent re-occurrence.

Corrective Actions for 2B
The firm reviewed 350 QC logbooks and found only the logbooks listed in the observation had not undergone review in the required timeframe. The firm opened deviation FRAD20E0749; determined the root cause and updated associated documents to prevent re-occurrence.

The above corrective actions were reviewed without comment.

EXHIBITS COLLECTED

Exhibit No.	Document Description	Pages
1	Photographs taken during the inspection burned onto a CD and placed into a sealed Form FDA 525.	N/A
2	Electronic records provided by the firm on a USB flash drive placed in a sealed FDA Form 525	N/A
3	Inspection Presentation	28
4	Site Master File	56
5	Firm FDA registration	2
6	Genzyme supporting sites FDA registrations	1
7	Firm employees who participated in inspection	7
8	Firm employees present at inspection closeout meeting	1
9	Firm ICHQ3D overview for specialty care products	10
10	ICHQ3D risk assessments for specialty care products	124
11	Cell Bank Manufacture Memo	1
12	Thyrogen BSB validation overview	4
13	Thyrogen 160 L Bioreactor process validation report# 02-2427FR	16
14	Thyrogen Blue elute hold time validation report# 02-2429FR	10
15	Thyrogen Cell Expansion Validation Report #02-2288FR	26
16	Thyrogen single use technology validation report# 02-2463FR	28
17	Thyrogen purification process (not BSB)	1

18	Firm SOP index	20
19	Building 51 Floorplan	1
20	51 NYA EM monitoring procedure FBL-SOP-000826	44
21	Photographs taken by firm	32
22	Firm pictures from FIT tester# 3000242	5
23	FIT tester#3000242 printouts for SFO-1378345 and SFO-1390916	2
24	SOP FBL-SOP-001011 - Operation of the (b) (4) (b) (4) Tester	67
25	Thyrogen manufacturing record showing required use of (b) (4) (b) (4) (1041-05)	2
26	MES Logbook entry for (b) (4) SFO-1378345	1
27	Planned activities for OCT2022 shutdown of building	5
28	Thyrogen BDS lots manufactured since JAN2020	1
29	SOP BQ-GOP-000300 - A risk based approach to audit trail review for computerized systems V3	13
30	SOP BQ-GOP-000300 - A risk based approach to audit trail review for computerized systems V2	15
31	Form BQ-FRM-000899	4
32	Data integrity assessment for (b) (4) testers and CAPA 354658	16
33	SOP FBL-SOP-000635 - GxP Evaluation and Electronic Records_Signatures Assessment	24
34	Deviation FRAD22E0608 - (b) (4) Tester##3000242	3
35	Photograph of unknown brown residue wiped from BSC-2074	2
36	Thyrogen manufacturing record showing use of BSC# FB-2074 for lot# BGF1S11	6
37	SOP FBL-SOP-000709 - Walk-through procedure for Framingham Biologics	57
38	SOP BG-BOP-000260 - Walk-through inspections	13
39	June EAC walkthrough for bioreactor room (b) (4)	2
40	May2022 (b) (4) walkthrough of APT Cell Culture Areas	10
41	May2022 (b) (4) walkthrough of APT downstream purification	10
42	Firm memo of pH deviation FRD22E0331	12
43	Deviation FRAD22E0607 for QC retain samples	13
44	Corrective actions initiated by firm	16
45	Firm corrective actions to 2017 discussion items	46
46	Firm corrective actions to 2020 FDA 483 and discussion items	52
47	(b) (4) Error Email	2
48	FBL-SOP-000698 Certification of HEPA Filters	24

ATTACHMENTS

Attachment No.	Document Description	Pages
Attachment 1	Form FDA 482 issued on 7/18/2022	3
Attachment 2	Form FDA 483 issued on 7/25/2022	2
Attachment 3	Amendment# 1 - Form FDA 483 issued on 7/25/2022	2
Attachment 4	FDA surveillance site dossier	5

Daniel L. Zheng -S
Digitally signed by Daniel L. Zheng -S
Date: 2022.08.17 16:08:42 -04'00'

Sean R. Marcsisin -S
Digitally signed by Sean R. Marcsisin -S
Date: 2022.08.18 06:56:56 -04'00'