DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857 ORAPHARMInternationalResponses@fda.hhs.gov OPMABLAInspection483Responses@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	21-25, 28-31 August 2023 & 01 Sept 2023 FEI NUMBER 3010479596

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Keith A. Ellis, Vice President QA Department

FIRM NAME	STREET ADDRESS
Samsung Biologics Co., Ltd.	300, Songdo bio-daero, Yeonsu-gu
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Incheon, 21987, Korea (the Republic of)	Drug Manufacturer

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

OBSERVATION 1

The Manufacturing Scientific Analytical Technology (MSAT) laboratory used in support of application submission testing data had inadequate controls over data integrity. Specifically,

A) The MSAT laboratory was used in support of application submission data for (b) (4) [redacted] and (b) (4) [redacted] with the laboratory a development laboratory having inadequate controls in assurance of data integrity since 2013. Although you conducted an internal data integrity assessment for each application, with completion of the assessments conducted during the inspection period, there is no means of determining with absolute certainty the true reliability of all test data, with a third-party independent assessment of the test data not performed.

B) An assessment to determine how the use of the MSAT lab in support of submission data to the Agency affects already commercially marketed products has not been completed. Data integrity deficiencies were identified in DEV-010168, which included, but is not limited to, shared administration passwords, lack of data backup, and lack of audit trails. This laboratory was identified as being used to generate data which was submitted to the Agency in support of currently approved drug products for (b) (4) [redacted]

C) Under Deviation Report 010168, Failure to correct integrity gaps and inappropriate GMP practices in the MSAT Laboratory, you indicate the first internal audit of the MSAT Laboratory was (b) (4) [redacted] as an ad-hoc audit (SIR(b) (4) [redacted]-05), and while no data integrity issues were identified, a recommendation to implement good documentation practice and data verification procedures was identified. At the request of Senior Quality Management, a subsequent audit was performed (b) (4) [redacted] (SIR-(b) (4) [redacted]-05), based on laboratory areas of work that included GMP requirements (e.g., support of regulatory submissions), with a critical observation pertaining to shared administration accounts and lack of data backup. Corrective action for shared accounts included the introduction of equipment logbooks to guarantee the minimum documentation requirements, with improper implementation. An audit (SIR(b) (4) [redacted]-06) of the laboratory was conducted again on (b) (4) [redacted]

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	[signatures]	Jeffrey F. Rosenwald, Consumer Safety Officer Dolores Mayayra, Consumer Safety Officer Wayne Seifert, Consumer Safety Officer Hyung-yul Lee, Pharmaceutical Scientist Jacob Gerhel, Lead Laboratory Scientist	09/01/2023

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with observations found in 2021 similarly found again, excluding logbooks. Although you opened CAPAs in response to the (b) (4) audit, the scope of the remediation plan did not fully assess data integrity gaps, focusing solely on traceability of equipment users, with no action taken for shared administrative passwords.

You received observations and recommendations from a client audit 06 July 2022 and 01 September 2022 specific to the MSAT Laboratory data management practices, with Samsung senior executive tour of the MSAT Laboratory 14 September 2022 identifying sticky notes with system password written on PCs, use of shared administration account, no label on chemical solutions, uncontrolled spreadsheets used to track samples, use of uncontrolled sheets to document test results, poor housekeeping of the laboratories, and safety issues. The same similar findings were reported through the MSAT internal audits conducted (b) (4) (SIR(b) (4) -05) and (b) (4) (b) (4) (SIR(b) (4) 06).

You failed to address laboratory deficiencies in a timely manner in assurance of data quality, data integrity used in regulatory submissions.

You further failed to notify clients in a timely manner, where the MSAT laboratory deficiency was identified in September 2022, with dates of client notification ranging from 17 October 2022 to 16 January 2023.

OBSERVATION 2
Written production and process control procedures are not followed, established, or are deficient. Specifically,

A) On 25 August 2023, observed for Plant (b) (4) RABS Fill Line (b) (4) Batch # (b) (4) was the transition of the (b) (4) stopper bowl from Grade B space into the Grade A RABS. Furthermore, observed was the transition of a (b) (4) system from Grade B space to the Grade A RABS, where the (b) (4) bag was opened in Grade B space, with the (b) (4) bag transitioning into the Grade A RABS. In both fill line setup activities, a portion of the (b) (4) bag entered the RABS Grade A space. On 30 August 2023, a similar observation was made during a review of the Fill Line (b) RABS smoke pattern video under GENP-02057. Observed was the opening of the (b) (4) bagged stopper bowl in Grade B space, with the (b) (4) bag transitioning to the RABS Grade A space that included a majority of the (b) (4) bag. SOP-MFE-00293, "Operation and Maintenance of (b) (4) Drug Product Vial Fill Machine", v40.0, Effective date 29 August 2023 fails to provide adequate instruction for transition of (b) (4) bagged sterilized equipment from Grade B space to the Grade A

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		Jeffrey P. Raimondi, Consumer Safety Officer Douglas F. Mackenzie, Consumer Safety Officer Hyung-Yul Lee, Pharmaceutical Scientist	09/01/2023

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RABS, where the (b) (4) bag should remain in Grade B space. You indicated that the smoke pattern video is reviewed and approved by quality, with the video used for training of fill line operators for proper RABS setup, aseptic technique.

B) Video recordings of media fill runs are not always retained. Procedure: SOP-MFP-00164, "Process Simulation for Drug Product" version: 37, Effective Date: 28-July-2023, states all personnel involved in aseptic operations will review excerpts of media fill video with Quality and Operations management and that any poor aseptic technique identified are discussed and provided remedial training to rectify poor aseptic technique. The videos for media fills dated 22-June-2021 (batch (b) (4) and 23-June-2021 (batch (b) (4) are no longer kept by the firm and are not available for viewing.

C) Your procedure, MET-00018, "Quantitation of Viable Microorganisms by Contact Plates", Effective Date 07/08/2023, version 43.0 Section 8.2.1.9 states "For personnel gloves monitoring, using Finger Dab Method - Aseptically open the contact plate and place his/her fingers with the glove gently on the media surface of one (1) contact plate (dabbing four (4) finger pads on (b) (4) and then rolling motion of thumb ensuring the entire pad of the thumb touches the surface of the media)". On 23-Aug-2023, we observed two of your aseptic operators fail to follow your procedure for fingertip personnel monitoring. Operators were observed testing the tips of their fingers instead of their finger pads during the aseptic filling of sterile injectable drug product, (b) (4) Lot (b) (4)

D) On 24 August 2023, observed was the (b) (4) drug substance fill process, batch (b) (4) into (b) (4) liter bottles by closed filling system. According to SOP-MFP-00074, "Inspection of Process Equipment and Materials", v22, Effective date 08 August 2023, Section 8.1 includes visually inspect materials, probes, parts, and assemblies before use or installation and verify that it is integral and free of debris, surface anomalies, foreign residue, or defects. Observed was no visual inspection of the drug substance container closure systems for absence of defect or debris within each bottle that could have an impact on product quality, with the standard operating procedure not followed. There is no documentation requirement for the drug substance container closure system visual inspection.

E) According to SOP-MFE-00280, "Recipe and Preparation for Sterilization using DP (b) (4), v49.0, Effective date 25/08/2023, Section 7.7 includes inspection for sterilization, check the (b) (4) of (b) (4) items while unloading the (b) (4) items onto the cart and/or shelf. The procedure fails to include at a minimum the

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rejection of the (b) (4) load if observed (b) (4)

F) SOP-QC-00130, "Assay Performance Monitoring" (ver.15.0, effective on 30 Jun 2022) does not include monitoring parameters for the methods of which performance monitoring was originally waived, but is needed (i. e. (b) (4) SEC and Binding ELISA methods) and does not include a justification for not assigning monitoring parameters, for the methods of which performance monitoring was originally waived (i.e., (b) (4) Peptide Mapping, (b) (4) HCP, HCD and (b) (4) methods).

G) On 24-Aug-2023, observed within Building (b) (4) Drug Substance Fill (b) (4) Grade C space and gowning (b) (4) was a (b) (4) respectively, with the top surface observed in an unclean condition. SOP-MFP-00012, "Room Cleaning and Sanitization Procedure", v84.0, Section 6.10 and 6.10.1 includes each department responsible for the cleanroom such as manufacturing (e.g., DS, DP, (b) (4) Dispensing, Sampling MDF) must clean and sanitize inner/outer surfaces, including the top and rear of (b) (4) (b) (4) EM carts and tools in the clean room. Difficult to reach areas that includes but is not limited to the top and rear side of control panels, (b) (4) bottom of (b) (4) etc. may include step stool/step ladder for cleaning and sanitizing high areas such as the top of (b) (4) (b) (4) or (b) (4) You failed to follow the procedure.

OBSERVATION 3
Controls over manufacturing operations and process have not been adequately established. Specifically,

A) Airflow visualization studies have not been performed for all interventions as required by procedure: SOP-MFP-00206, "Airflow Visualization Evaluation", Version: 8.0, Effective Date: 26-June-2023. The removal of jammed vials at the (b) (4) and the removal, adjustment/maintenance, and re-installation of the (b) (4) (b) (4) have not been evaluated as part of smoke studies.

B) Fill Line (b (b) (4) for drug product manufacture includes a (b) (4) vial conveying system, where (b) (4) vials filled with drug product can be filled and pending stoppering during a line stoppage. There is no procedure or HMI limitation for how long product filled vials can be exposed to the filling environment pending stoppering nor is there a requirement for a time-period to be assessed by media fill. Your Quality Risk Assessment fails to assess the said condition and impact on product quality.

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C) MBR-00570, MBR-573, and MBR-00934 do not clearly describe the frequency of the visual inspection for bioreactor surface followed by (b) (4) for the following unit operations: (b) (4) Operation of (b) (4) L Bioreactor, (b) (4) Operation of (b) (4) L Bioreactor, and (b) (4) Operation of (b) (4) L Bioreactor.

OBSERVATION 4

Revalidation of equipment used in the processing of drug product is not performed at appropriate intervals. Specifically,

A) Your firm's Quality Unit failed to ensure equipment is maintained and used within its validated state. For example:

(b) (4) ID 130-(b) (4)-5311: Was due on 01-Jul-2022. However, the equipment was not revalidated until 21-Sep-2022. Your firm produced (b) (4) batches using items that were (b) (4) within this time using this equipment.

-(b) (4) ID 130(b) (4)-3220: Was due on 02-Dec-2021. However, the equipment was not revalidated until 16-Feb-2022. Your firm produced (b) (4) batches using items that were (b) (4) within this time using this equipment.

(b) (4) ID 130(b) (4)-3210: Was due on 02-Dec-2021. However, the equipment was not revalidated until 03-Jan-2022. Your firm produced (b) (4) batch using items that were (b) (4) within this time using this equipment.

-HPLC ID 150-HPLC-001: Was due for revalidation (b) (4) from the last revalidation which was performed on 20-Aug-2023. However, this equipment was observed being used past its revalidation due date.

-HPLC 150-HPLC-006: Was due for revalidation (b) (4) from the last revalidation which was performed on 16-Aug-2023. However, this equipment was observed being used past its revalidation due date.

-ELISA Binding ID 150-FACS-003: Was due for revalidation (b) (4) from the last revalidation which was performed on 03-Aug-2023. However, this equipment was observed being used past its revalidation due date.

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Your firm stated the equipment were not revalidated due to their respective grace periods granted by your procedure SOP-VAL-00016, Revalidation Program, Effective date: 07-Jul-2023, Version 51.0; however, you were unable to provide scientific justification to support the grace period.

B (b) (4) 230-(b) (4) -5311 used in Plant (b for (b) (4) sterilization of equipment and components for Fill Line (b) includes a (b) (4) supplied with (b) (4) , with the last (b) (4) sterilization process validated both physically and biologically, June 2020. The (b) (4) is not revalidated on a routine basis in assurance the validated state is maintained.

OBSERVATION 5

The Quality Unit is inadequate to ensure it is capable of carrying out it's roles and responsibilities. For example:

A) The Quality Unit has not ensured quality records such as deviations and non-conformance investigations are closed within their respective due dates. Between Quarter 1 2022 and Quarter 2 2023 the average amount of overdue deviation and non-conformance investigations were 10% and 18%, respectively.

B) SOP-QC-00105, "Invalid Assay Procedure" (ver. 22.0, effective on August 18, 2023) allows for up to (b) (4) consecutive failures for the same sample for select methods. Multiple invalid runs, including consecutive runs (high invalid assay rate), were reported for (b) (4) and (b) (4) (MET-00274 - (b)%) and for (b) (MET-00717 - (b)% and MET-00718 - (b)%). In addition, laboratory investigations for SST failures did not identify abnormalities using PEMME (people, equipment, method, material, environment) tool and investigations concluded that invalidation rate will be monitored continuously since root cause of invalid runs was not identified. This is a repeat observation as high invalid rates were previously observed during FDA inspection of the facility in 2022 and corrective actions implemented by the firm appear not effective.

C) Investigations opened to review environmental monitoring in which sterile drug products are filled are inadequate. For example, your firm opened deviation DEV- 010542 due to a recovery of Paenibacillus glucanolyticus a spore forming microorganism during the filling of sterile drug product, (b) (4) Lot (b) (4) . However, your firm failed to extend the investigation to other personnel involved in the filling of this drug to ensure the interventions performed by other personnel did not impact the sterility of the drug product.

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	[illegible]	[illegible], Consumer Safety Officer [illegible], Consumer Safety Officer [illegible], Consumer Safety Officer Hyung-yul Lee, Pharmaceutical Scientist [illegible] Scientist	09/01/2023

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Additionally, during the inspection, we observed that personnel monitoring is not performed according to your procedure. See OBSERVATION 2C.

OBSERVATION 6

Facilities are not adequately maintained. Specifically,

A) On 25 August 2023, observed was a ceiling port cover dislodged in Grade B space, directly over where Plant (b) (4) (Fill Line (b) (4) RABS (b) (4) open. The condition was observed during fill line setup for manufacture of (b) (4), Batch # (b) (4).

B) On 21 August 2023, observed within the GMP warehouse, Solid Waste Collection WI-1130 was a door leading to the outside, with the door bottom damaged. Furthermore, in Office Supply WI-1131, a floor receiving and loading ramp dock mechanism was missing a seal. Each condition is a potential entry point for pests to enter the facility.

C) On 21 August 2023, a deteriorated sealant between floor and wall was observed in (b) (4) Preparation room (b) (4) in Plant (b)

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