DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
CDER/OPQ/OPMA/DPMA VI 10903 New Hampshire Avenue; White Oak Building 51/Room 2269 Silver Spring, MD 20993-0002 E-mail: OPMABLAInspection483Responses@fda.hhs.gov	07/22/2024-07/30/2024
	FEI NUMBER 3010479596
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED Gail Ward, EVP of Quality Center	
FIRM NAME Samsung Biologics Co., Ltd.	STREET ADDRESS 300, Songdo bio-daero, Yeonsu-gu
CITY, STATE, ZIP CODE, COUNTRY Incheon, 21987, Republic of Korea	TYPE ESTABLISHMENT INSPECTED Drug Substance and Drug Product Manufacturer

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established, written, and followed.

Specifically,

A. Air flow visualization studies (smoke study) for the Plant (b) (4) Vial Filling line used to aseptically fill (b) (4) and (b) (4) drug products did not meet the acceptance criteria of airflow that is unidirectional and free from turbulence.

1) Video footages obtained during the smoke studies (Document # EVAL-ATT-03011, dated 11/14/2021) under operational conditions (dynamic) show air turbulence and upward flowing air near the area of (b) (4) where open vials are sorted after exiting the (b) (4) (b) (4)

2) Smoke study videos show air turbulence and upward flowing air near the conveyor belt transferring open vials from (b) (4) to filling station.

3) Smoke study videos show air turbulence above stopper (b) (4) and stopper bowl.

4) The smoke study videos show that the smoke manifold is positioned at fixed locations inside the RABS. The air flow visualization studies have not thoroughly evaluated the entire area inside the RABS. For example, there are gaps between adjacent HEPA filters and between the RABS barrier to the edge of HEPA filters. These areas have not been thoroughly assessed during the smoke studies.

5) The smoke studies to demonstrate airflow from filling room into Grade B corridor during critical (b) (4) operations such as (b) (4) installation did not allow thorough evaluation of the impact of the operations to airflow in the area.

B. Poor aseptic techniques were observed during the manufacturing of (b) (4) drug product (b) (4) batch number (b) (4) on 07/25/2024.

1) At 11:31 am, during (b) (4) assembly installation, grade A operator took a pair of

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE *(Print or Type)*	DATE ISSUED
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scissors positioned outside of Grade A area to cut open the (b) (4) wrap of the (b) (4) assembly in the RABS.

2) Between 11:39 am to 12:00 pm, the (b) (4) assembly was placed on the countertop surface in the RABS system. The (b) (4) connecting to the filling line made direct contact with non-sterile counterton surface. At 11:46 am and 14:08 pm, Grade A operator was observed to hold the (b) (4) connecting to the filling line with gloved hands after the gloved hands touched non-sterile parts in the RABS system.

3) Operator was observed removing the (b) (4) before placing the exposed (b) (4) in the (b) (4) holder. He then reached over the (b) (4) to place the tubing in the slot in the (b) (4) holder. The same operation was repeated (b) (4) times to install (b) (4) Operator was observed to break "first air" over the exposed (b) (4)

4) Grade A operator's shoulder was observed to touch the (b) (4) glove (b) (4) near the filling station during post-aseptic setup personnel monitoring.

5) At (b) (4) during filling operation an operator was observed extending the (b) (4) glove over the capping turn station containing stoppered but not capped (b) (4) vials to remove jammed caps. The vials were not discarded.

C. Aseptic processing system and procedures are not designed to prevent potential microbiological contamination.

1) While performing personnel monitoring (PM), operator who performed sampling was observed to spray his/her gloved hands with disinfectant. He/she proceeded to open the media plate while both gloved hands were still wet with disinfectant.

2) A total of (b) (4) portable tablet devices are used in the Grade B filling room. No protection or over wrap were rendered during filling operation.

3) Trash bin with unsmooth surfaces is placed in Grade B filling operation staging area.

4) Sprinklers connecting to potable water supply system are installed in DP filling room and grade B corridor. Leakage monitoring, cleaning/disinfection, and microbial monitoring of the sprinkler system are not implemented.

5) QA personnel responsible for monitoring aseptic behaviors during drug product aseptic filling operation or media fill studies are not required to be present on the operation floor.

D. Environmental monitoring of aseptic processing areas following aseptic assembly of filling components and aseptic filling operations is deficient. For example,

1) Microbiological surface samples are not taken from the (b) (4) and stoppering station.

2) The fingerprint collection of operators was not done properly (*e.g.*, without rolling on the contact plate) during post-operation personnel monitoring. Personnel monitoring did not include sampling of Grade A operator's goggles.

OBSERVATION 2

Written records of investigations into unexplained discrepancies do not always include appropriate conclusions and follow-up.

Specifically,

A. During June 2022 to June 2024, there were 181 deviations initiated for (b) (4) drug substance. Your investigations attributed the root-cause for 95 (52.5%) out of these deviations to human errors, with awareness training proposed as the primary corrective action and preventive actions (CAPA). Your firm failed to conduct adequate root-cause analysis by thoroughly assessing the relevant process, equipment, and quality systems so that effective and sustainable CAPA(s) can be implemented. In addition, the root causes of 50% deviations for (b) (4) DS initiated in 2024 were deemed to be human errors, indicating continuing of the deficient deviation investigation practice.

B. Deviation #014509 was initiated for an action level excursion of personnel monitoring (PM) samples collected from Plant (b) (4) DP, Sterile Staging Zone (DP- (b) (4) Grade B) on 15/03/2024, (b) (4) CFU/plate obtained; Action Level: ≥ (b) (4) CFU/plate, sum of (b) (4) PM samples). The deviation was deemed "recurring", but classified as "minor". Only an "awareness training" was given to the impacted operator. There was no further action taken. The operator continued performing aseptic operation in the DP production without aseptic technique requalification. According to SOP-MFP-00063 (Aseptic Gowning Qualification and Aseptic Qualification for DP, version 21), aseptic qualification will be disqualified only if an operator exceeds (b) (4) personnel monitoring action level within (b) (4)

C. Deviation #010977 was initiated for an action level excursion from Air Viable collected in (b) (4) DP Sterile Staging Zone (DP (b) (4) Grade B) on 04/02/2023, (b) (4) CFU/m^3 obtained; action level ≥ (b) (4)

CFU/ m^3). The root-cause for this "recurring" event was attributed to "*dissemination of the microorganisms due to the hasty actions*" since the sampler had to leave the room after starting the sampling due to "*physiological trouble*". No CAPA was taken to address the significant deviation from fundamental principle of GMP. In addition, there was no thorough performance evaluation of the GMP work conducted by the impacted analyst.

D. Environmental monitoring (EM) Out of Trend (OOT) investigation #OOT-002020 was initiated on 27/10/2023 for a mold alert from a routine EM sample in (b) (4) DP (b) (4) Zone (DP (b) (4) Grade B). The investigation was concluded with no root-cause identified. No CAPA was initiated. The investigation is deficient in that it failed to assess the prior mold OOTs in 2023, including OOT-001974 (03OCT2023; 25Sep2023), OOT-001896 (20Jul2023), OOT-001819 (16May2023); OOT-001793 (03May2023), OOT-001704 (02Feb2023), for potential recurring mold issues in the (b) (4) DP manufacturing facility.

E. Your investigation into DEV-014685 designated the deviation as minor. Upon interviewing the analyst, it was found that QC analyst aborted testing runs without adequate supervisor and QA involvement. QA deviation investigation failed to identify the true root cause.

F. Investigations of aborted endotoxin runs are inadequate. Specifically,

1) Invalid Run records #IR-005802 (6/24/2021), IR-009589 (10/3/2023), IR-009790 (11/5/2023), IR-011056 (7/20/2024) documented that the endotoxin testing runs were aborted due to OD graph abnormality or software error (frozen system). The samples were tested in other working equipment while the frozen systems were rebooted by QC analysts with no QA notification. No further investigations were conducted to identify the root-cause of the software error and there were no appropriate CAPAs to prevent the recurrence of events.

2) Invalid Run records #IR-009042 (06/24/2023), IR-009736 (10/27/2023), IR-009835 (11/10/2023), IR-011016 (7/11/2024) documented the aborted runs due to system frozen errors. Instrument vendor performed repairs based on instrument manual. However, the repairs appeared ineffective to prevent the recurrence of the events. Two aborted runs (IR-009736 and IR-009835) occurred on the same equipment (b) (4) QC-MPR-3016) with the same repairs performed within two weeks. In addition, no requalification of the repaired instrument was performed and there is a lack of documentation on the details of the repairs.

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OBSERVATION 3

Written procedures for production and process controls designed to assure that the drug product has the identity, strength, purity, and quality that they are purported or represented to possess are not fully established or followed.

Specifically,

Your program for the visual inspection (VI) of sterile (b) (4) drug products does not provide adequate assurance that finished products possess their purported quality attributes, including that they are free from particulate matter and critical defects. This is evidenced by:

A. Visual inspection information contained in Executed Batch Records do not conform with the visual inspection SOP for Manual Inspection Procedure for Liquid Product (SOP-MFP-00028, V 54.0, effective date 06/28/2024). Specifically, under section 7.4.18, it is senior inspector's responsibility to perform the classification for defect vials per SOP-MFP-00104 Defect Criticality Classification and Defect Library, after the defect vials have been identified by individual inspectors. The same information was also confirmed by your VI SME and supervisor. However, based on Vial Inspection Log for Products in Executed Batch Records for drug product (b) (4) (Batch number (b) (4) (b) (4) vial defect classifications were recorded by individual inspectors.

B. Your visual inspection qualification program is managed by the same team which performs routine 100% visual inspection under drug product manufacturing department. For example,

   1) Drug product VI supervisor who manages the (b) (4) 100% visual inspection operations is in charge of the VI test sets used for qualification and (b) (4) requalification of DP VI inspectors.

   2) The answer keys to the qualification test sets are kept in an unlocked cabinet in the office area where DP VI inspectors are seated.

   3) According to VI supervisor, senior inspectors are responsible for the design and administration of the qualification and (b) (4) requalification exams for DP VI inspectors. Senior inspectors also participate in drug product 100% visual inspection.

OBSERVATION 4

Your firm has not established adequate procedural controls to protect electronic data acquisition and manufacturing control systems.

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A. Management of access controls is inadequate for computerized systems. For example,

1) There is no assurance that access to Empower 3 chromatography data system (CDS) is always controlled with unique username and password. Usernames such as "testadmin", "CQ_TEST", and "system" are assigned to administrator role. Administrator account "testadmin" was used to delete multiple QC projects between 02/13/2023 and 02/02/2024.

2) According to your SOP for Administration of Empower 3 Chromatography Data Management System (SOP-QC-00430, V7.0, effective date 03/29/2024), QC analyst and reviewer are allowed to calibrate and quantitate data, view quantitation fields, and view numerical and textual results in the review window before the testing run is complete and prior to data processing. Your SOP also grants QC analyst the privilege of "Saving Processing Methods" which effectively allows the analyst to create new processing methods and/or modify existing processing methods including all parameters in any section of the processing method.

3) User privilege settings configured in the manufacturing control system for the Plant (b)(4)DP (b)(4) (equipment # 230-(b)(4)3120) allow "Supervisors" to "clear project data".

4) User privilege settings in the manufacturing control system for the Plant (b)(4)DP (b)(4) (equipment # 230(b)(4)-5311) allow "Supervisor/Maintenance" to "set date/time".

B. Not all injections in the analytical runs are processed to report results. For example, under project (b)(4) 2097 injections were made while only 1329 results were reported; under project (b)(4) 354 injections were made and only 290 results were reported.

C. Your firm operates (b)(4) non-viable particle (NVP) monitoring equipment to perform non-viable particle counting during environmental monitoring in support of grade A/B drug product manufacturing. You do not back up the raw data generated and stored on the equipment. Per your SME, the data capacity storage for the (b)(4) NVP is up to (b)(4) tests, after which the oldest data are overwritten and lost if not backed up. At this time the equipment does not have adequate data management, archival, and retrieval of record capabilities.

D. Your firm uses computer software 32Karat and iCE3 to run multiple QC testing methods such as Determination of Purity by CE-SDS under Non-Reducing Condition and Examination by Imaged Capillary Isoelectric Focusing (iCIEF). The testing raw data are processed and reported by CDS software Empower 3. There is no assurance that all data generated by 32Karat are captured, processed, reported by Empower 3.

E. QC projects were deleted from Empower 3 system without proper control. For example,

1) Six hundred eighty-nine (689) projects were deleted on 10/12/2021 due to project migration and restoration error. No deviation investigation was raised to address the error.

2) Sixteen (16) projects were deleted by system administrator between 2021 to 2024 for reasons including incorrect project (three projects), duplicate project (one project), typo error (three projects), and wrong directory (nine projects). QA was not aware of such deletion and there is no assurance that raw data were not deleted because of the project deletions.

OBSERVATION 5

There is a lack of assurance that your drug substance and drug product manufacturing operations are appropriately designed to ensure the prevention of contamination of equipment or product by environmental and processing conditions that would be expected to have an adverse effect on product quality.

Specifically,

A. Your firm's new product introduction process including multi-product manufacturing risk assessments are not based on health-based exposure limits (HBELs) such as Acceptable Daily Exposure (ADE) or Permitted Daily Exposure (PDE) values, determined by qualified toxicologists from available toxicological and pharmacological data. For examples, ADE/PDE values were not evaluated for (b) (4) of the (b) (4) products that were introduced into the Plant (b) (4) Sterile DP manufacturing facility.

In addition, your firm has not performed appropriate protein degradation or inactivation studies to demonstrate that the disinfectants utilized for facility/equipment decontamination (including RABS) can effectively reduce the residues of products introduced to your DP manufacturing facilities from non-product contact surfaces to acceptable levels.

B. There is a lack of assurance that your cleaning procedures for product-contact process equipment in your DS manufacturing facilities are effective in preventing cross contamination. For example,

1) The (b) (4) used to swab the shared process equipment during the cleaning validation and cleaning verification, have not been validated for their intended use.

2) Your cleanability evaluation and (b) (4) rinse/swab recovery studies in

support of cleaning validation do not include representative soils from the (b) (4) drug substance manufacturing processes, such as (b) (4) and (b) (4) production run, cell containing) cell culture media.

C. You have not established an adequate environmental monitoring (EM) program to ensure that your facility cleaning and sanitization procedures are effective in preventing microbial contamination. Specifically, there is a lack of adequate justification for the surface sampling locations in the Grade D areas of the DS and DP manufacturing facilities. For example,

1) (b) (4) floor surface sampling (b) (4) location is selected for the Bioreactor Hall (Grade D) in Plant (b) (4) DS manufacturing facility. There are no surface samples taken from walls of the facility.

2) A total of (b) (4) of surface sampling (b) (4) locations are selected for all grade D manufacturing areas in Plant (b) (4) DP manufacturing facility. Among these surface samples,
   - (b) (4) surface sample is taken from door handle or work surface from each of the following areas: (b) (4) (b) (4) (b) (4) (b) (4)
   - (b) (4) floor surface sample is taken from each of the following areas: (b) (4) (b) (4) (b) (4) (b) (4) (b) (4)
   - Limited floor samples are taken from corridors with no samples taken from walls.

3) A total of (b) (4) surface samples (b) (4) are taken from all grade D areas from Plant (b) (4) DS manufacturing facilities.

Your 2023 and 2024 EM trend reports have shown mold recoveries in Grade A/B DP manufacturing areas of Plant (b) (4) and recurring bacterial spore recoveries in DS manufacturing areas of Plant (b) (4) and Plant (b) (4)

OBSERVATION 6

Laboratory controls used to release (b) (4) drug substance (b) (4) and (b) (4) drug substance (b) (4) and drug product (b) (4) exhibit high rates of system suitability tests failures. Specifically,

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A total number of invalid runs for Host Cell DNA method MET-01143 (b) (4) Determination of Residual DNA by Real-time PCR (v1.0) was (b) (4) out of (b) (4) % invalid rate) in (b) (4) laboratory and (b) (4) out of (b) (4) % invalid rate) in the (b) (4) laboratory, due to failed system suitability criteria. In addition, a total number of invalid runs for Potency ELISA method MET-00274 (b) (4) ELISA (v6.0) was (b) (4) out of (b) (4) % invalid rate) in (b) (4) laboratory. Laboratory investigations for SST failures not always identified 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. There is no assurance that the methods are capable of consistently meeting system suitability acceptable criteria.

OBSERVATION 7

You have not fully validated the use of all (b) (4) production bioreactors for (b) (4) drug substance (b) (4) manufacturing process in SBL Plant (b) (4)

Specifically,

The SBL Plant (b) (4) cell culture facility is equipped with (b) (4) bioreactor (b) (4) (b) (4) production bioreactors for a total of (b) (4) production bioreactors. You have deemed all bioreactors equivalent based on identical design and qualification and the manufacture of (b) (4) drug substance can occur using any of the (b) (4) bioreactors. The total number of production bioreactors which can be used to manufacture (b) (4) drug substance is (b) (4) (b) (4) out of (b) (4) bioreactors were used in the process performance qualification studies. Commercial manufacturing occurred in additional (b) (4) bioreactors. However, there are no manufacturing process data for the remaining (b) (4) bioreactors to support the use of these bioreactors for the manufacture of (b) (4) drug substance.

OBSERVATION 8

Standard operating procedures and/or protocols are not followed, established, or adequate.

Specifically,

A. SOP-MFE-00760 ver. 16.0 does not provide adequate instructions to collect (b) (4) samples from sampling valve SV- (b) (4) to check (b) (4) During collection of the first sample. (b) (4) was allowed to trickle down on the side of the vessel. Subsequently, while (b) (4)

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and sampling for the second sample, the bottom part of the sampling tube was dipped into the waste bucket liquid.

B. Section 6.1.14.1 of SOP-QC-00086, Control of Quality Control Laboratory Equipment, ver. 65.0 indicates that if equipment specification or model number is different from the previously installed units, and is to be used for non-compendia methods for data generation purpose (such as, HPLC, CE, GC, Plate Reader, AAS, FPLC, UV, FT-IR, etc.), method validation addendum study is required. However, based on the Quality Risk Assessment of QC methods (QRA-02975) used for the purpose of analytical methods transfer from (b) (4) Laboratory to (b) (4) Laboratory, for non-compendial methods, based on the QRA risk scoring and considerations for various factors (e.g., analyst, complexity, equipment, environment etc.) comparability runs for majority of assays were not deemed to be required.