DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Division of Biotechnology Manufacturing 10903 New Hampshire Avenue, White Oak Building 51 Room 2269, Silver Spring, MD 20993 E-mail: OPMABLAInspection483Responses@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	August 22-August 30, 2022
	FEI NUMBER 3011248248

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Kiran Kumar Gandhirajan, Senior Vice President and Site Head

FIRM NAME	STREET ADDRESS
Biocon Sdn. Bhd.	No. 1, Jalan Bioteknologi 1, Kawasan Perindustrian SiLC
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Iskandar Puteri, Johor, Malaysia 79200	Drug Substance and Drug Product Manufacturing Facility

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

OBSERVATION 1

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

A. There is no assurance that your aseptic process simulation studies or smoke studies performed in RABS are representative of the conditions during routine aseptic setup or filling operations. For example, we observed a RABS (b) (4) open for longer than (b) (4) during setup. We also observed three RABS (b) (4) open at the same time during filling operations. Neither of these activities were simulated in media fills or smoke studies. In addition, the assembly of the (b) (4) stopper insertion (b) (4) and the tightening of the (b) (4) stopper (b) (4) were performed differently from what we observed in the smoke studies.

B. A third RABS (b) (4) was opened to start active air sampling and left inadvertently open during Line (b) (4) Installation.

C. We observed an operator contacting fixed equipment parts inside the RABS and RABS (b) (4) without spray sanitizing with (b) (4)

D. We observed operators spraying their gloves and resuming operations inside the RABS before letting them dry completely.

E. We observed operators sanitizing the top surface of a (b) (4) bag containing sterile equipment yet subsequently touching both sides of the (b) (4) bag during installation.

F. We observed the operator blocking unidirectional laminar flow by leaving an opened (b) (4) bag in the RABS that had a large surface area.

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	Anjali Shukla Hamet Touré	Richard Ledwidge, Senior Biologist Anjali Shukla, Lead Interdisciplinary Scientist Hamet Touré, Regulatory Officer Santos Camara, Consumer Safety Officer	08/30/2022

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G. The goggles used by operators in the aseptic filling area have three open vents on the top of the goggles.

H. We observed an operator often moving abruptly and rapidly inside the RABS and during (b) (4) wipe down of the RABS (b) (4)

OBSERVATION 2
There is a lack of assurance that your cleaning procedures, used for non-product-contact process equipment in the RABS, is validated to prevent contamination. Specifically,

A. The cleaning of the RABS and fixed equipment inside the RABS is performed manually. There is no assurance that cleaning is performed in the same manner as the cleaning validation study performed in December 2016.

B. The (b) (4) validation disinfectant efficacy study for (b) (4) o support RABS decontamination coverage was not performed in the Grade A RABS.

C. Cleaning verification is performed only on product-contact equipment surfaces in the RABS at the conclusion of drug product production. There is no verification of the cleanliness of hard to reach surfaces on non-product contact equipment inside the RABS.

OBSERVATION 3
Your firm's quality unit's oversight of your GMP manufacturing and laboratory operations is inadequate. Specifically,

A. You use the European Pharmacopoeia (Ph. Eur.) reference standard (b) (4) as your quality control reference standard for release and stability testing of your (b) (4) drug substance and drug product. There are no written procedures to ensure that the Ph. Eur. (b) (4) eference standard continues to be suitable for use, once the standard is under the purview of your QA oversight in your manufacturing facility.

B. The final finished packaged and labeled (b) (4) drug product is not tested for identity and thereby does not ensure the identity of (b) (4) and discrimination from the other (b) (4) drug products manufactured in the facility.

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C. The external laboratory qualification and audit failed to ensure that the contract testing firm appropriately qualified the bioidentity test. This USP bioidentity test is included in the (b) (4) drug substance specifications.

D. Your procedure BM/QA/SOP/036 Handling of Out of Specifications- Analytical fails to specify that a batch with a confirmed out-of-specification result, assigned to a manufacturing process-related cause, must be rejected.

E. Your procedure BM/QCA/SOP/096- Sampling, failed to establish time limits for sampling of refrigerated raw materials performed at 18-25 °C in which case unspecified time-out-of-refrigeration may adversely impact the raw material quality.

F. Insufficient justification for the use of (b) (4) non-compendial raw material was provided.

OBSERVATION 4
Deviation investigations are inadequate. Specifically,

A. You failed to adequately identity the source of glass particulates in (b) (4) olution batch failures (b) (4) and (b) (4) According to the firm, glass particulates can arise from vial breakage or glass friction at different points during drug product and (b) (4) solution manufacturing. From July 2021 to 2022 for drug product batches filling in (b) (4) the critical defect percentage due to glass particles varied, but were occasionally detected from > (b) (4) % of total batch size. The source of the glass particulates is still not known. The inability to identify a root cause is exacerbated by the fact that there is no assurance that vial breakage will be detected by the operator or critical alarm systems.

B. Your firm failed to adequately implement appropriate CAPAs for OOSs. For example during the dispensing of DS (b) (4) Working Cell Bank Lot # (b) (4) during inoculum transfer, a passive monitoring plate was found to be out of specification limit in grade A biological safety cabinet. The organism identified was the same as the host organism being transferred into vials. The 6 M root cause investigation determined it was a method issue. The CAPA implemented was to add the identified (b) (4) strain to the automated (b) (4) identification system library. This occurred for BM/OOS-01/20/019, BM/OOS-01/20/021

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and BM/00S-01/19/052.

C. Your firm failed to adequately identify the root cause of (b) (4) clogging of (b) (4) n drug product batch number (b) (4) As described in deviation PRID# 43977, your firm implemented a new (b) (4) with a larger (b) (4) surface area to lessen clogging; however, the firm has not identified the true cause of the (b) (4) (b) (4) clogging in order to implement appropriate CAPAs.

OBSERVATION 5
There is lack of assurance that water and (b) (4) used in the manufacture of (b) (4) drug substance manufacturing processes is suitable for its intended use. Specifically,

A. The (b) (4) drug substance (b) (4) L. fermenter media uses (b) (4) grade water which does not meet the USP acceptance requirements for (b) (4) water of conductivity < (b) (4) mS/cm @ 25 °C, pH (b) (4) total organic carbon (TOC) < (b) (4) ppm, and aerobic microbial count < (b) (4) CFU/ml. The internal specification limits for the (b) (4) water on the site does not test for conductivity and the acceptance criteria for pH, TOC, and aerobic microbial count are widened to pH (b) (4) TOC < (b) (4) ppb, and TVAC < (b) (4) CFU/ml respectively. The (b) (4) water is tested for the absence of objectionable microorganisms S. aureus, P. aeruginosa, E. coli, and Salmonella species.

B. Your risk assessment evaluating the appropriateness of the use of the (b) (4) water in your (b) (4) DS manufacturing process is inadequate. The risk assessment focuses on the minimal water requirements for biotechnology manufacturing and not on water quality attributes to support the (b) (4) fermentation process and potential impacts on product quality.

C. Your risk assessment regarding the addition of (b) (4) compounds to your (b) (4) system is inadequate because it does not fully assess the potential levels of the additives to your process or the ability of your process to eliminate the additives.

D. The "Process (b) (4) delivered to the facility from the (b) (4) system has not been tested (b) (4) for critical physical qualities to ensure sterilization ((b) (4) The (b) (4) ransfer pipes have a length greater than (b) (4) from the points of use and have never been sanitized.

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OBSERVATION 6

Your batch record documentation practices are inadequate. Specifically,

The batch records for drug substance (DS) (b) (4) batches (b) (4) had numerous correction footnotes including those for error entry, overwriting, incorrect justifications, calculation errors, incorrect volumes, illegible handwriting, incorrect column entries, incomplete time, transcription errors, incorrect date, and incorrect spelling.

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