DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857 E-mail: ORAPHARMInternational483responses@fda.hhs.gov	08/11/2022-08/12/2022 08/15-19/2022; 08/26/2022
	FEI NUMBER 3003981475

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Mr. Ganesh D. Reddy, Global Head – Biologics Manufacturing

FIRM NAME	STREET ADDRESS
Biocon Biologics Limited	Bommasandra-Jigani Link Road
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Bengaluru, Karnataka, India 560099	Drug Substance & 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 and followed.

Specifically,

A. During the (b) (4) Filling Line and the (b) (4) Vial Filling Line fill activities on Monday, August 15, 2022, Production operators were observed having RABS (b) (4) during donning and intervention activities over drug product filled (b) (4) and empty vials (pre-drug product), respectively. All (b) (4) and vials were further processed to be included in the batch, and were not discarded. This activity was noted for (b) (4) nj. (b) (4) IU (Batch (b) (4) and (b) (4) (b) (4) Injection (b) (4) IU (Batch (b) (4) drug products, on their respective fill lines.

B. During both setup and filling activities for both filling lines, setup of sterile components were not always performed aseptically to protecting first air or prevent cross contamination. Specifically,

1. During the (b) (4) Vial Filling Line setup on Tuesday, August 16, 2022, of the sterile stopper (b) (4) bowl, (b) (4) and transfer device, some operations (e.g. (b) (4) levice (b) (4) removal over stopper (b) (4) required the operators to perform manipulations over sterile components and violate first air principles.

2. During (b) (4) Filling Line and (b) (4) Vial Filling Line activities, on Friday, August 12, 2022, and Tuesday, August 16, 2022, respectively, primary (clean) and secondary (soiled) Production operators were observed handling common items (e.g. (b) (4) bottle, scissors, pens) interchangeably when conducting Grade A and Grade B operations during open RABS (b) (4) setup interventions.

3. The secondary Production operators, responsible for sanitizing the (b) (4) Filling Line RABS (b) (4) following open (b) (4) interventions, prior to closing, with (b) (4) did not (b) (4) the (b) (4) wipes after (b) (4) cleaning stroke.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	Arsen Karapetyan	Michael R. Shanks, Senior Biologist Arsen Karapetyan, INV-Dedicated Drug Cadre Ralph M. Bernstein, Biologist Zhong Li, Sr. Pharmaceutical Quality Assessor	08/26/2022

4. During (b) (4) Filling activities and (b) (4) Vial Filling activities on Friday, August 12, 2022, and Monday, August 15, 2022, respectively, Production operators were observed with their hands down by their sides, below their waist.

5. During (b) (4) Filling activities on Friday, August 12, 2022, operators were observed wearing goggles having gaps between goggle strap and operator's head during the aseptic operations. Goggles used by operators to protect against exposed skin while working in the grade A & B areas during aseptic operations having unprotected gaps are not an effective barrier against a source of particles generated by, and microorganisms shed from, the face.

6. Aseptic behavior deficiencies in items B.1 through B.4, were also noted during the review of the smoke studies, BF/QA/STY/R/130, ver. 5.0, effective date 04/15/2021, Report for Air Flow Pattern Study of the Laminar Air Flow Stations in Vial Filling Line (b) (4) in Biocon Formulation Area (b) (4) and B1/QA/AFVR/002, ver. 3.0, effective date 08/02/2021, Report for Air Flow Visualization Studies for the Aseptic Laminar Air Flow Stations in Biocon Fill-Finish Area – (b) (4)

C. Environmental and personnel monitoring of aseptic processing areas following critical Grade A filling operations are deficient. Specifically,

1. During RABS (b) (4) environmental monitoring (b) (4) filling activities on Monday, August 15, 2022, for the (b) (4) Vial Filling Line, EM DAB plate samples were not taken from both sides of the RABS (b) (4) Following the EM monitoring, the (b) (4) use of these RABS (b) (4) was observed during a new run setup activity on Tuesday, August 16, 2022, on the (b) (4) Vial Filling Line, with (b) (4) n the same RABS (b) (4) port (F2-GPF-005).

2. During the routine environmental monitoring following aseptic filling activities, not all sanitized, non-sterile equipment surfaces above sterile filling and stoppering components (direct and indirect product contact) on the (b) (4) Vial Filling Line were sampled. For examples, microbiological surface samples were not taken from sensor assemblies (devices) and stopper (b) (4) body.

3. During the routine aseptic filling process, the designated Grade A (ISO 5) area where the (b) (4) conveyor is located on the (b) (4) Vial Filling Line is not subject to Non-Viable-Particulate (NVP) monitoring.

D. BPDR 2728121, initiated on April 5, 2022, that conducted aseptic behavior corrective actions from its assessment, and the CAPAs from the Grade A environmental monitoring excursions of Media Fills noted below, were not adequately assessed by the Quality Assurance system from a global Biocon Biologic aseptic behavior perspective to effectively curtailed this aseptic behavior citation.

1. Report BF(b) (4)/APS-LF/R/016, ver. 1.0, effective date 02/24/2022, Report for Aseptic Process Simulation Batch No. (b) (4) (MFG Date: December 2021) for (b) (4) Process on Liquid Fill Vial of (b) (4) Line Finish Facility.
2. Report BF(b) (4)/APS-CT/R/015, ver. 1.0, effective date 02/28/2022, Report for Aseptic Process Simulation Batch No. (b) (4) (MFG Date: January 2022) on (b) (4) Line of (b) (4) Line Finish Facility.
3. Report BF(b) (4)APS-LF/R/031, ver. 1.0, effective date 08/16/2022, Interim Report for Aseptic Process Simulation Batch No. (b) (4) MFG Date: July 2022) on Liquid Fill Vial Line of (b) (4) Line Finish Facility.

OBSERVATION 2

Your firm's facilities are not adequate to ensure the prevention of contamination of equipment or product by environmental conditions that could reasonably be expected to have an adverse effect on product quality.

Specifically,

A. You have not taken effective corrective actions to adequately address the persistent trend of fungal contamination in your Site-(b) (4) Drug Substance Block manufacturing facility. From April 27, 2022 to June 21, 2022, your environmental monitoring program repeatedly recovered fungi from (b) (4) DS areas as reported in the (147) OOAC (Out of Action Level) excursions. Since then, additional (16) OOAC excursions with fungal recoveries have been reported and are still under investigation. You have not conducted a thorough assessment of the scope of the fungal contamination in the facility and the potential routes by which fungi had entered your classified manufacturing areas.

B. Your firm's environmental monitoring (EM) program does not include appropriate measures to monitor, trend and control fungal contamination in your DS and DP manufacturing facilities.

Specifically,

1. Appropriate OOAL (Out of Alert Level) and OOAC limits have not been established for fungal contamination in the Grade C and Grade D areas. Only a cumulative account of bacterial and

fungal colonies is evaluated against the OOAL/OOAC limits for the classified areas. Consequently, your EM program lacks assurance of a timely and sensitive detection of adverse trend of fungal contamination in your facilities.

2. There is no trending of fungal contamination in the facilities. In addition to "A" above, the following fungal contaminations were reported in other Site (b) (4) DS and DP manufacturing facilities:

   a. There are more than (20) OOAC excursions with fungal recoveries reported for (b) (4) DS manufacturing facilities from May 14, 2022 to June 27, 2022.

   b. OOAC# BF/OOAC/21/253 was initiated for a fungal contamination ((b) (4) CFU/plate) found on a settling plate sample in a Grade B area.

   c. OOAC# BF/OOAC/21/255 was initiated for a fungal contamination ((b) (4) CFUs) found on a personnel (b) (4) monitoring (finger dab) sample.

   d. OOAC# BF/OOAC/21/362 was initiated for a fungal contamination (b) (4) CFUs) found on a surface monitoring of a vial-filling machine (b) (4) sample.

   e. OOS# MM-OOS-M-FP-21-003 was imitated for a fungal contamination (b) (4) CFU/10 mL) found in a (b) (4) bulk DS batch # (b) (4)

C. Your firm lacks an established cleaning and sanitization program to prevent the introduction of microbial contamination into controlled manufacturing environments in your Site (b) (4) drug substance and drug product manufacturing facilities. Specifically,

1. Your cleaning and sanitization procedures for the classified DS and DP manufacturing areas including aseptic cores, S2/BT/MC/SOP/0024, S2/BF/FM/SOP/0039, and S2/BF/FM/SOP/0194 do not require documentation and verification that the surfaces are wetted and remain wetted for the contact time validated in the disinfectant efficacy studies (DES).

2. Your disinfectant efficacy study, BF/QCQS/STY/R/313 (effective 15-Nov-2017), does not adequately support the sanitization procedures for the antimicrobial and sporicidal effectiveness of the disinfectants and sporicidal agents for all representative manufacturing surfaces in the (b) (4) DS manufacturing facility. For example, glass (windows) and materials used for cart-wheel tread/core were not included in the study.

3. Your disinfectant efficacy study, PL/MB/VR/21/001-01 (approved 30-May-2022), does not do not adequately support the sanitization procedures for the antimicrobial and sporicidal

effectiveness of the disinfectants and sporicidal agents for all representative manufacturing surfaces in the (b) (4) DP, and (b) (4) DS manufacturing facilities. For example, (b) (4) and cart-wheel tread/core materials were not included in the study.

4. The (b) (4) program with (b) (4) used to as a remediation measure for bioburden control of classified manufacturing areas after media-fill failures, EM excursions, and major facility events (b) (4) power failures, construction, etc.) has not been validated to demonstrate the effectiveness of the (b) (4) process to disinfect the cleaning rooms in (b) (4) and (b) (4) Fill-Finish manufacturing facilities [refer to Report no. BF/QC/STY/R/289].

D. Your firm's facility and equipment are not of adequate design or in an adequate state of repair. The following concerns were noted during the current inspection:

1. The following were observed in the (b) (4) DP fill-finish facility:
   a. The Vial Washing Room (b) (4) a GMP controlled environment (Grade D), in not maintain in an adequate state to facilitate appropriate cleaning in that the wall-ceiling interface caulking above the (b) (4) does not have smooth cleanable surfaces.
   b. There is no caulk sealant on the backside of an insulated pipe in Room (b) (4) that may promote microbial egress into the control area (Grade D).
2. The following were observed in the (b) (4) DS (b) (4) manufacturing facility:
   a. Chipped and cracked floors, which make them difficult to clean, were observed throughout the grade C and D areas in the facility.
   b. The (b) (4) surfaced floors in Room (b) (4) grade-C (b) (4) purification and (b) (4) suite, had been repainted with a surfacing paint-like material that was uneven, rough, and appeared hard to clean. Several movable carts in the room had had their wheels painted to the floor, obstructing the ability to clean the floors under the carts.
   c. In Room (b) (4) portable carts had multiple signs of damage, including flaking and chipped paint, wheels with worn or damaged surfaces, making them hard to clean.
   d. Throughout the grade D and C areas in (b) (4) there were non-sanitary sockets that potentially opened to the interior of the wall or to other rooms.
   e. In Room (b) (4) the (b) (4) motor for the (b) (4) apparatus was rusted, pitted and corroded, making it difficult to clean.

f. There were no low return HVAC grilles for the grade (b) (4) in the facility.

OBSERVATION 3

Written records of investigations into unexplained discrepancies and the failure of a batch or any of its components to meet specifications do not always include the conclusions and follow-up.

Specifically,

A. Investigations initiated and performed by your Quality Unit in response to out-of-specification test results related to testing related to drug substance and drug product manufactured are not always scientifically sound or comprehensive. Specifically, Corrective Action/Preventive Action (CAPA's) as a result of investigations are not always comprehensive to address root causes documented to have been performed. For Example:

1. OOS No. MM-OOS/A/FP/20/099, dated 11/30/2020: During IEX-HPLC Chromatography analysis of (b) (4) Bulk product Batch Number (b) (4) for stability test at 24 months LT, test result for IEX-HPLC was found to be OOS for % basic, with result as (b) (4) % versus specification of NMT (b) (4) %. Initial test was performed on 11/23/2020, with OOS initiated on 11/20/2020. Per your firm, the original sample was not used for hypothesis testing in support of your firms suspected root cause as poor column performance due to sample solution stability being expired, "analyst not available" and "waiting for approval from the firm's partner" for this product. Instead, hypothesis testing was performed on 01/25/2021, more than 2 months after the OOS, using new sample preparations, with within specification results used to justify repeat analysis, after which the initial OOS result was invalidated.

2. OOS Numbers MM-OOS/A/I/20/004 (dated 07/27/2020), MM-OOS/A/I/20/006 (dated 08/04/2020), MM-OOS/A/I/20/007 (dated 08/10/2020), and MM-OOS/A/I/20/008 (dated 08/19/2020) were initiated for (b) (4) DS Batch Number (b) (4) OOS for particle count test by (b) (4) in-process), prior to (b) (4) filtration of the bulk solution. Your investigation determined that all OOS results were valid, with CAPA explained as this OOS was prior to (b) (4) m filtration activities. This DS batch was further used for manufacture for drug product, which was distributed in the domestic market. There is no justification for relying on additional manufacturing controls as a CAPA, without review of environmental monitoring procedures and controls which may have led to the in process OOS results.

3. Starting from 08/03/2020 to 12/13/2021, approximately eight different OOS investigations were initiated for (b) (4) Injection USP, (b) (4) IU/ml (b) (4) development batches,

where out of specification results were observed during analysis of samples of stability for (b) (4) in (b) (4) test. Multiple CAPA's were initiated and executed over an approximate 1.5 years, including revision of batch manufacturing records to manually reject (b) (4) when (b) (4) stops, revision of dispensing of raw materials, (b) (4) verification, impact of (b) (4) hold time in (b) (4) and impact of (b) (4) concentration on (b) (4) CAPA PR ID 9734 was documented to be completed and closed as of 07/04/2022, however, your firm has not identified a long term CAPA effectiveness check strategy for ongoing testing for (b) (4) during (b) (4) testing for this product.

4. From 09/23/2021 to 03/31/2022, at least three out of specifications results have been observed for "(b) (4) content" for (b) (4) Suspension and Injection USP (b) (4) IU/mL, (b) (4)

   - OOS/A/FP/21/060, dated 09/23/2021, was initiated for process validation batches (b) (4) and (b) (4) with OOS results of (b) (4) mg/ml and (b) (4) mg/ml versus a revised specification of versus a specification of (b) (4) to NMT (b) (4) mg/ml (b) (4) – (b) (4) % of target (b) (4) mg/mL). Based on the laboratory investigation, no assignable/probable root cause was identified for the reported OOS for (b) (4) and wrong input (b) (4) lot number for (b) (4) with both results invalidated. As a result, the specification was widened to (b) (4) ng/ml to NMT (b) (4) mg/ml (b) (4) % to (b) (4) % of target (b) (4) mg/mL). As a result, your firm performed an assessment of the (b) (4) raw material lot to determine actual concentration of (b) (4) for specific lots versus (b) (4) mg/ml theoretical content.

   - OOS/A/FP/21/065, dated 10/04/2021, was initiated for batch (b) (4) 36 Month Long Term stability test, with OOS result as (b) (4) mg/ml versus a specification of (b) (4) to NMT (b) (4) mg/ml (b) (4) – (b) (4) % of target (b) (4) mg/mL). Root cause was determined to be (b) (4) (b) (4) content test specification limit. As a result, the specification was widened to (b) (4) mg/ml to NMT (b) (4) mg/ml (b) (4) % to (b) (4) % of target (b) (4) mg/mL).

   - Although the specification was widened, your firm encountered an additional OOS/A/FP/21/099, dated 03/31/2022, was initiated for batch (b) (4) 6 Month Accelerated sample, with OOS result as (b) (4) mg/ml versus a specification of (b) (4) mg/ml to NMT (b) (4) mg/ml (b) (4) % to (b) (4) % of target (b) (4) mg/mL), with root cause determined to be "analytical variability". Your firm's corrective actions with respect to the OOS investigations do not appear to be adequate and justified, in that, not only does your firm

perform an assessment of each material received for actual (b) (4) content, but your firm also widened the gap from "(b) (4)% to (b) (4)%" to "(b) (4)% to (b) (4)%", only to register another OOS.

5. OOS Investigations were initiated for (b) (4) units (b) (4) for test item (b) (4) for process validation batches (b) (4) (OOS BF/OOSMD-21-003, dated 10/21/2021), (b) (4) (OOS BF/OOSMD-21-004, dated 10/25/2021), (b) (4) (OOS BF/OOSMD-21-005, dated 11/13/2021), (b) (4) stability test (OOS BF/OOSMD-21-006, dated 01/08/2022), and (b) (4) stability (OOS BF/OOSMD-21-007, dated 01/11/2022) with acceptance criteria of "the maximum (b) (4) shall be less than or equal to (b) (4) Between all OOS results, total number of OOS observed included 12 (b) (4) out of (b) (4) with values ranging from (b) (4) to (b) (4) Your firm's proposed corrective actions included exploring (b) (4) testing method, which is still an open topic, along with the CAPA to "perform a confirmatory test of failed (b) (4) with a fresh (b) (4) for (b) (4) time only and if the confirmatory test results are failing to meet acceptance criteria, then suitable QMS shall be logged and investigation shall be performed". A CAPA to invalidate an initial OOS result and not initiated an OOS investigation is not adequate.

6. During the inspection, we reviewed at least nine (9) microbiology out of specification investigations initiated over the past approximate 2 years, from 08/21/2020 to 06/20/2022 (OOS Numbers MM-OOS/M/CS/20/003, MM-OOS/M/CS/20/020, MM-OOS/M/CS/21/001, MM-OOS/M/CS/21/010, MM-OOS/M/CS/21/011, MM-OOS/M/CS/21/012, No. MM-OOS/M/CS/21/013, No. MM-OOS/M/CS/21/005, No. MM-OOS/M/CS/22/003) regarding (b) (4) rinse samples after cleaning operations for bioreactors including, but not limited to (b) (4) (b) (4) located in your (b) (4) building. In most investigations, OOS results were TNTC/100mL for equipment components versus a specification of (b) (4) CFU/100mL.

   - As early as 02/2021, CAPA PR# 19348 was initiated for revision of bioburden testing procedure to incorporate more detailed testing procedure for sanitization practices to be followed, however your firm continued to have this root cause for OOS results. In addition, CAPA PR# 14276 was initiated to assess the bioburden limits, (b) (4) CFU/100mL against manufacturing cleaning verification limit of (b) (4) CFU/100mL, as your firm discovered that the (b) (4) CFU/100mL limit was incorrect for cleaning verification limit and should have been assigned as (b) (4) CFU/100mL as the cleaning verification. CAPA # 14276 was used to invalidate most OOS results. There is no justification for using this CAPA to invalidate most

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OOS results, with an implied specification of (b) (4) CFU/100mL instead of (b) (4) CFU/100 mL, where the OOS results were over (b) (4) CFU/100mL, with most OOS results reported as TNTC. As a result of these OOS investigations your firm identified the following microorganisms on or around your equipment in the (b) (4) building: *Sphingomonas paucimobilis, Cronobactor sakazkii, Chryseobacterium Indologenes, Paenibacillus glucanolyticu, Phyllobacterium myrsinacearum, Mycrobacterium flavescens, Delfia acidovarans, Pseudomonas flurescens, Staphylococcus xylosus, Bacillus cereus, Burkholderia contaminans, Burkho Ideria contaminans, Serratia marcescens, Ralstonia picketti,* and *Micrococcus luteus.*

B. The (b) (4) purification process in building (b) (4) experienced 9 events of bacterial contamination in the drug substance (DS) (b) (4) and formulated bulk prior to (b) (4) um (b) (4) drug substance (DS) filtration. These DS lots were filled and released for DP manufacturing. Specifically, in 2021, Biocon building (b) (4) drug substance (DS) purification (b) (4) experienced eight (8) bacterial contamination excursions wherein the intermediate (b) (4) and pre (b) (4) um filtration (b) (4) as detailed in deviation report(s) 200018, 14747, 15068, 15182, 27719, 29251, 30630, 37271), and one (1) post formulated intermediate DS prior to (b) (4) um filtration and (b) (4) DS fill (see report 4602). The (b) (4) were found to be contaminated with a range of bacteria (including *C.indologens* (3 repeats), *S.maltophila* (4 repeats), *S.multivorans*, *D.nishinomiyaensis*, *K.sedentarius*, *S.spiritivorum*, *C.testosteroni*, *D.acidovorans*, *S.marcescens*, and *A.baumannii*) at levels above the bioburden assay action limit of (b) (4) CFU/10mL, including confluent lawn(s) or spreader lawn(s) (reported as 101 colonies), or too numerous to count (TNTC). These DS lots were filled into DS containers and released to drug product (DP) manufacture. The impact of these contamination events for the DS or derived DP lots' stability was not adequately assessed.

C. The (b) (4) purification process in building (b) (4) experienced three (3) events of bacterial contamination with *Burkholderia contaminans* in the formulated bulk drug product prior to (b) (4) filtration (deviations 21-042, 22-003 and 22-032). These lots were aseptically filled and released. The impact of these contamination events for the DP lots was not adequately assessed.

D. During the (b) (4) filling machine assembling for drug product '(b) (4) (b) (4), Batch No. (b) (4) on August 12, 2022, noticeable amount of (b) (4) (b) (4) was observed dripping out of the (b) (4) stopper bowl that was sterilized through an (b) (4) load # A2/220776 and installed on the line. The assembling process was put on hold.

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The (b) (4) stopper bowl was removed from the line, re-cleaned, re-sterilized through an (b) (4) load # A2/220779. and then re-assembled on the filling machine. The assembling and filling processes for (b) (4) were continued and completed. There was no action taken to the other filing machine parts that were sterilized through the same (b) (4) load # A2/220776. Deviation QMS # 81533 was initiated with pending investigation on root-cause-analysis, final product impact assessment, and corrective action and preventive action as of August 26, 2022.

OBSERVATION 4

Deviations from written test procedures and laboratory mechanisms are not recorded and justified.

Specifically,

Your Quality Unit has not been effective in carrying out its duties of ensuring that drug products are manufactured in accordance with current good manufacturing practices (cGMP) to ensure safety, efficacy, purity, and overall quality of drug substances and drug products manufactured at your firm. This is demonstrated by a cascade of failures in your Quality Unit responsibilities related to controls on review of laboratory testing data, conducting investigations, and conducting activities per written procedures. The inspectional observations listed on this form document that your firm and/or consultants have not performed the adequate assessments/reviews to ensure the quality of drug substances and drug products manufactured and tested at your firm. For Example, but not limited to:

A: During our review of your Empower 3 chromatography software, interrupted sequences were observed, which generated "Data Incomplete" and "Bad Checksum" chromatographic data. Your firm's Quality Control Unit documented these interrupted injections as laboratory incidents, showing that no chromatogram had been generated, however, your Quality Unit was not aware that the software has the capability to verify the incomplete data and evaluate whether the sample did run, and if so, view the chromatogram. During our review of HPLC data, we reviewed electronic data for finished product, drug substance, in-process, stability, and raw material testing, where interrupted injections were requested to be verified (brought back) and reviewed: We observed several instances where repeat injections and additional testing may have been performed in contradiction to your firm's data integrity procedure. We observed interrupted sequences involving the following products and batch numbers, some of which were shipped to the US Market:

	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
SEE REVERSE OF THIS PAGE		Michael R. Shanks, Senior Biologist Arsen Karapetyan, INV-Dedicated Drug Cadre Ralph M. Bernstein, Biologist Zhong Li, Sr. Pharmaceutical Quality Assessor	08/26/2022

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Product Name	Batch Number	Type of test	Type of sample/ Injection name	Laboratory Incident Number.
(b) (4)		(b) (4) content	Finished Product/ Sample	QC/Q13/LI/22/0069
		Purity by SEC-HPLC	Analyst Qualification/ Laboratory standard	QC/Q17/LI/20/0016
		Purity by IEX-HPLC	Column performance/ Laboratory standard	QC/Q17/LI/20/0048
		Peptide Mapping by HPLC	Drug substance/ System Blank	QC/Q8/LI/22/0420
		Purity by SEC-HPLC	Stability/ (b) (4) vater	QC/Q8/LI/21/0817
		Purity by IEX - HPLC	Drug Product/ Sample	QC/Q8/LI/20/0521
		Purity by IEX HPLC	Stability/ Sample	QC/Q8/LI/20/0365
		(b) (4) content by HPLC	In-process/ Sample	QC/Q8/LI/21/0546
		Purity by SEC - HPLC	In-process/ Sample	QC/Q8/LI/22/0374
		Purity by IEX HPLC	Stability/ IEX: Standard	QC/Q8/LI/20/0455
		(b) (4) content by HPLC	Drug substance/ Sample	QC/Q8/LI/20/0525
		Peptide mapping By HPLC	Drug substance/ Sample	QC/Q8/LI/21/0398

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		Michael R. Shanks, Senior Biologist Arsen Karapetyan, INV-Dedicated Drug Cadre Ralph M. Bernstein, Biologist Zhong Li, Sr. Pharmaceutical Quality Assessor	08/26/2022

As a result, during review of such cases, the interrupted sample injections were not adequately documented to be performed in your laboratory incident reports, and calculations were not performed to determine whether the interrupted test injections were within specification or out of specification, where applicable. During multiple interrupted sequences, after the data was brought back (verified) during the inspection, a full run time with all principal peaks eluted for the sample solution was observed. Additionally, your firm has not demonstrated that you understand the different types of communication errors and circumstances which may lead to a "Data incomplete" or "Bad Checksum" chromatography. This discrepancy in your firm's ability to review, document, and investigate all electronic data is a gap in your firm's Data Integrity Program. As of the close of the current inspection, your firm has not initiated a deviation with respect to the incomplete data interrupted sequences observed during the inspection.

B: On or around 08/14/2021, during a routine walkthrough inspection by your firm's site QA in the Bioassay laboratory QC-Q8 in (b) (4) block facility, an intact/unopened sample of (b) (4) (b) (4) mg Batch (b) (4) (2 Months Accelerated Stability), received for testing of Inhibition of Proliferation assay by (b) (4) cells (Biological activity), was observed to be present in the sample storage refrigerator, however testing records indicated that the analysis for this sample had been completed and the batch had been released to the India Market. As a result, Event 39548, dated 08/16/2021 and QMS Deviation 41034, dated 08/27/2021 were initiated, with subsequent investigation revealing that a total of six (6) commercial batches and nineteen (19) stability time points samples (b) (4) samples). The investigation revealed that in lieu of testing the samples, analysts tested a reference standard instead. Per your firm's investigation, root cause factors included inadequate sample storage practices, shortage of manpower due to high attrition for qualified analysts, COVID impact, and analyst behavior. In response, your firm performed various laboratory risk assessments and data integrity assessments with the support of in-house compliance and external consultant support. Our review of these assessments found them to be inadequate: Specifically, your firm has at least (b) (4) different laboratories, and the retrospective review of data was not extended to all pertinent laboratory equipment with respect to the data integrity aspect of this investigation. For Example, your assessment of equipment in other laboratories did not identify HPLC/GC equipment as an equipment or system for review of data, however during the current inspection we identified significant gaps with the review of electronic data with respect to HPLC/GC testing operations.

OBSERVATION 5

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12420 Parklawn Drive, Room 2032 Rockville, MD 20857 E-mail: ORAPHARMInternational483responses@fda.hhs.gov	08/11/2022-08/12/2022 08/15-19/2022; 08/26/2022
	FEI NUMBER 3003981475

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
Mr. Ganesh D. Reddy, Global Head – Biologics Manufacturing	
FIRM NAME Biocon Biologics Limited	STREET ADDRESS Bommasandra-Jigani Link Road
CITY, STATE, ZIP CODE, COUNTRY Bengaluru, Karnataka, India 560099	TYPE ESTABLISHMENT INSPECTED Drug Substance & Drug Product Manufacturer

Your firm's quality unit's oversight of your GMP manufacturing and laboratory operations are inadequate.

Specifically,

A. Your oversight of your primary (b) (4) reference standard is inadequate. You utilize USP issued (b) (4) DS as your quality control (QC) primary reference standard for your (b) (4) (b) (4) vials, and (b) (4) vials, intended for release to the US market. You do not know the USP (b) (4) reference standard expiration date. You do not have a written and QA approved stability protocol for the USP standard, which is required once the standard is under the purview of your QA oversight in your manufacturing facility.

B. Your oversight of the (b) (4) analytical assessment procedure is inadequate. Your analytics labs that are responsible for the (b) (4) assessment of multiple proposed (b) (4) drugs, i.e., (b) (4) (b) (4) did not perform a verification of the sample(s)' identity to be tested by the analysts, for any of the (b) (4) assessment analytics. In contrast, your QC labs verifies the analysts' possession of an analytic sample with a two person written verification.

C. Your oversight of critical GMP Q13 sample incubation chambers are inappropriate. Your keys to the Q13 mezzanine 2-8°C stability chambers and 2-8°C retain chamber are stored in an unsecured container, in an unlocked drawer, in the Q13 mezzanine stability facility. (b) (4) individuals have access to the room, along with seven (b) (4) from Engineering & Maintenance.

D. Assurance of the identity of, and discrimination between, (b) (4) DS grades and types, utilized for US market and the rest of world (ROW), are not appropriately controlled. The Biocon facility in Bengaluru (3003981475) manufactures multiple (b) (4) DPs intended for different markets. The (b) (4) DS utilized in these DP are manufactured at your Biocon (b) (4) (b) (4) facility. The Biocon (b) (4) facility manufactures (b) (4) DS with multiple product codes, which indicate the different manufacturing processes and different (b) (4) DS quality. These product codes are the only system used to prevent the (b) (4) DS to be utilized for the ROW and the proposed US marketed (b) (4) vials, (b) (4) (b) (4) and (b) (4) vials, from mix-ups. You do not currently have an analytic performed at your (b) (4) DP manufacturing facility which can discriminate between these different types and grades of (b) (4) DS. Thus, there is no assurance, by the process or by testing, that the correct (b) (4) DS is being used for the (b) (4) drug products to be marketed in the US in accordance with their specific (b) (4)

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E. Your quality unit does not fully exercise its responsibilities regarding the critical service contractor qualification. Specifically,

1. QA oversight of your vendor audits, and vendor status follow up and re-instatement, is inadequate. Biocon SOP C/GB/QA/SOP/0051 states in section 6.45, page 22/29, that a violative vendor may be blocked, but your re-qualification of a blocked vendor see section 6.46, page 23/29, does not adequately control for the resumed use of a previously blocked vendor. Section 6.46.4 states that a "CAPA and commitment letter" from the blocked vendor are sufficient to reinstate the violative vendor. There is no inclusion or mention in the procedure for a new Biocon on-site audit, or a meticulous Biocon analytical qualification of the previously blocked product, or service.

2. Your quality unit has not conducted any on-site audit of (b) (4) who is responsible for the validation of clean rooms in your Site (b) (4) drug substance and drug product manufacturing facilities.

3. Your quality unit has not qualified the suppliers of Biological Indicators (BIs), (b) (4) (b) (4) The BI's are used for the qualification of sterilization, sanitization, or decontamination processes in your Site (b) (4) drug substance and drug product manufacturing facilities.

F. Your (b) (4) drug product (DP) batch record instruction is not followed, and your procedures to prevent cross contamination of (b) (4) DP are inadequate.

During an Agency facility tour of the (b) (4) upstream (b) (4) drug product manufacturing process of DP batch (b) (4) and facility (b) (4) Formulation room, the Agency observed the preparation for the manufacture of (b) (4) solution (b) (4) The production operator aliquoted a sample of the (b) (4) from the process manufacturing tank into a (b) (4) nL (b) (4) tube. The operator tested the pH of the (b) (4) sample with a standard, bench top, pH meter. The pH meter was not sanitized or of a single use type. The operator then returned the tested (b) (4) sample back into the process manufacturing tank, which contains the (b) (4) solution (b) (4) (b) (4) to be filled into (b) (4) DP. This step of returning potentially cross contaminated material to the DP formulation is not in the (b) (4) solution (b) batch record, and could result in the contamination of the formulated DP.

G. There is no adequate data integrity program in place to include a statistically sound comprehensive review of all electronic data by the Quality Assurance Unit for standalone and network systems, to ensure completeness, consistency, and accuracy of all chromatographic and non-chromatographic

electronic data generated by the Quality Control Laboratory.

OBSERVATION 6

There is a lack of assurance that your cleaning procedures for the shared product-contact process equipment in your Drug Substance and Fill-Finish product manufacturing facilities, are effective in preventing cross-contamination.

Specifically,

A. The QC rinse recovery & swab recovery study (BF/QCQ13/AMV/R/076, version 001) does not include representative soils from the (b) (4) drug substance manufacturing process, such as unconditioned (unused) and conditioned (end of production run, cell containing) cell culture media. In addition, The study failed to include glass (for viewing port) for viewing ports that is swabbed during cleaning validation.

B. Your cleaning verification procedures for (b) (4) drug substance manufacturing equipment failed to include all surface (swab) samples from areas hardest to clean, such as (b) (4) valves, gaskets or O-rings.

C. Your cleaning verification procedures for (b) (4) drug product manufacturing equipment failed to include all surface (swab) samples from areas hardest to clean, such as bottles and caps.

D. Your manual cleaning procedure for product-contact filling machine parts in (b) (4) Fill-Finish, S2/BF/FM/SOP/0040 (version 4.0, effective 01-Aug-2022) does not define the (b) (4) rinse volumes that are required for accurate determination of product residue from a TOC rinse sample test result.

OBSERVATION 7

Laboratory controls do not include the establishment of scientifically sound and appropriate standards designed to assure that components and in-process materials conform to appropriate standards of identity, strength, quality and purity.

Specifically,

A. SOP # C/GB/QC/SOP/0069 "Guidelines for Integration in Chromatography and Electrophoresis" (version 6.0, effective 29-Jul-2022) (refer to Section 6.4.1) stipulates that "closely eluting peaks" or poorly resolved peaks are integrated using (b) (4) integration mode, which does not reflect the true area under the peaks. Your integrating in this manner disproportionately reduces the area

for the smaller peaks and consequently underestimates the relative amount of the smaller peaks, *i.e.*, the impurity peaks.

B. The QC standard testing procedure (STP) QC/Q8/SPEC/FP/159-01v003 utilized for the release and stability specification "microscopy test" for (b) (4) DP (b) (4) and (b) (4) DP vial does not describe the procedure that your QC analysts follow. The STP provided to the Agency instructs the analyst to measure the (b) (4) size of each (b) (4) using a micrometer throughout the slide. The analysts follow a procedure that instructs them to identify (b) (4) field with (b) (4) then to capture the field in the microscopy software, and to then measure (b) (4) and to record the (b) (4) shape and range (maximum and minimum length of the (b) (4)

OBSERVATION 8

Your firm has not established adequate procedural controls to protect the electronic data acquisition and/or manufacturing control systems used for DS and DP manufacturing in your Site (b) manufacturing facilities.

Specifically,

A. The computerized system (YOKOGAWA data logger; Model GP10, S/N S5WA12293), used to collect data during the calibration of QC instrument, temperature mapping and thermal validation of critical process equipment, has not been validated to protect original electronic records and relevant metadata (e.g., audit trails).

B. There is a lack of documented evidence that the computerized system, THEMA4 (version W44.3), that controls and collects data from (b) (4) 2 for the (b) (4) filling line in (b) (4) Fill-Finish facility, has been validated for data backup and retrieval. Audit trails enabled in the system are not reviewed for each data set during the batch review process. In addition, there is inadequate segregation of duties in the management of user privileges. The system administrators, responsible for control of the records generated by the system, are also the engineers responsible for the content of the generated records.

C. A system hardware upgrade for the SCADA chromatography system, M2-CS-4, in (b) (4) facility was performed in March of 2021. A revalidation of the software installed on the system, SIMA TIC WinCC Hotfix 2, was not completed prior to the use of the upgraded system for GMP operations in the facility.

OBSERVATION 9

Computer systems used in the testing of a drug product are not of appropriate design to facilitate operations for its intended use.

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NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Mr. Ganesh D. Reddy, Global Head – Biologics Manufacturing

FIRM NAME	STREET ADDRESS
Biocon Biologics Limited	Bommasandra-Jigani Link Road
CITY, STATE, ZIP CODE, COUNTRY Bengaluru, Karnataka, India 560099	TYPE ESTABLISHMENT INSPECTED Drug Substance & Drug Product Manufacturer

Specifically,

A. Your firm does not have adequate written procedures for conducting Initial Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ). Specifically, qualification activities were performed by your software vendors for networked Empower V3.0 software for HPLC equipment. Your firm appears to have performed Performance Verification for Empower, however this verification is not adequate, in that, it does not evaluate the consistent performance of the software/equipment over a specified period and operating environment. For Example, during our review of your Empower 3 chromatography software, interrupted sequences were observed, which generated "Data Incomplete" and "Bad Check Sum" chromatographic data. Your firm has not demonstrated to understand the different types of communication errors and circumstances which may lead to a "Data incomplete" or " Bad Checksum" chromatography.

B. Your firm maintains SOP S2/BF/QCM/SOP/0076, titled "Procedure For Review of CCTV the CCTV's installed in the microbiology laboratories in (b) (4) and (b) (4) Per this procedure, CCTV usage can be used to support OOS investigations by reviewing footage where "duration of the availability of the footage" is (b) (4) Your firm has not validated the CCTV software Milestone Xprotect Smart Client 2014 to depict that the software functions as purported in a consistent and accurate manner that is secure, reliable, and traceable. In fact, during the inspection, we reviewed two microbiology OOS investigations, OOS No. MM-OOS/M/CS/21/001 (dated 05/13/2021) and OOS No. MM-OOS/M/FP/22/001 (dated 06/07/2022) where CCTV footage was used in support of the root cause analysis which invalidated the OOS; however, all footage was automatically purged after (b) (4) and your does not have a process in place to save footage which was used in support of these investigations.

OBSERVATION 10

GMP Equipment is used outside its validated acceptance criteria for critically controlled material.

Specifically,

Quality Control Stability Chambers, QC-Q13-AI-141 and QC-Q13-AI-142, located in QC Building Q13, are validated for 2 – 8 °C and both have had numerous excursions from their validated temperature over the past two year. Additionally, these excursions have not triggered deviations to be opened.

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OBSERVATION 11

Your firm has not adequately qualified the critical utility used for the (b) (4) drug product manufacturing processes in the Building (b) Fill-Finish manufacturing facility.

Specifically,

The (b) (4) delivered to the facility has not been sampled at the points of use and tested for purity, impurities, and odor as specified in the USP-NF.

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