DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Division of Biotechnology Manufacturing; WO51 / Room 2269 10903 New Hampshire Avenue Silver Spring, MD 20993 E-mail: OPMABLAInspection483Responses@fda.hhs.gov	08/23/2022-08/26/2022 FEI NUMBER 3015283245

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

FIRM NAME	STREET ADDRESS
Biocon Biologics Limited	20th KM Hosur Road, Electronics City
CITY, STATE, ZIP CODE, COUNTRY Bengaluru, Karnataka, India 560100	TYPE ESTABLISHMENT INSPECTED Drug Substance 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

Your firm's (b) (4) drug substance (DS) manufacturing facilities on Biocon Site-(b) 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. The DS fermentation and cell (b) (4) manufacturing areas' classification are "unclassified and uncontrolled", or UNC. During the start of the inspection, your firm stated that the upstream system is a (b) (4) system, and, for this reason, there was limited concern regarding the control of the upstream manufacturing environment. However, your (b) (4) DS (b) (4) K fermenters have experienced at least four (4) failures due to microbial contamination since FY2020. The (b) (4) (b) (4) fermenters, as well as your cell (b) (4) (b) (4) procedures, are performed in uncontrolled and un-monitored environments. A window in the fermenter suite was observed (observed on 23 Aug 2022) open to the outside environment. Raw materials for the (b) (4) for your fermentation (b) (4) are weighed in uncontrolled LAF (laminar-air-flow) units and then, in the UNC, added to (b) (4) vessels that are open to the environment. Raw materials for the (b) (4) and (b) (4) unit operation (b) (4) are weighed in in uncontrolled and unmonitored environments, and added to (b) (4) preparation tanks in the UNC environment. No data have been provided to demonstrate that the contamination check test is able to recover contaminating microorganisms in the presence of the host cell organism. There is no microbial monitoring performed on the (b) (4) steps; the (b) (4) L transfer vessels utilized for the (b) (4) steps have inadequate (b) (4)

B. The DS downstream processing (DSP) facility maintenance and cleanliness are inadequate for GMP grade C manufacturing. During a facility walkthrough of your (b) (4) area, multiple deficiencies were noted. We observed soiled floors, cracked floors with peeling paint, damaged walls, excessive caulking, and other uncleanable surfaces.

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OBSERVATION 2

There is a lack of assurance that your downstream (b) (4) drug substance manufacturing operations are appropriated designed to prevent microbiological contamination of (b) (4) drug substance.

Specifically,

A. The (b) (4) unit operation is repeated at least (b) (4) times, each of which take approximately (b) (4) with no cleaning of the (b) (4) between lots. During a facility walkthrough inspection of the (b) (4) area, intended to observe (b) (4) (b) (4) removal, the operators removing (b) (4) intermediate were observed accidentally touching the (b) (4) from the (b) (4) with their gowning, and intentionally, with gloved hands. One operator opened the intermediate DS bag by using his gloved hands to slide them into the bag and open it. One operator leaned over the open (b) (4) repeatedly blocking the LAF. Operators deposited (b) (4) covered (b) (4) components on the parts trolly, and liquid spread from the (b) (4) from the (b) (4) parts in a pool that covered the operators' tools. The operators then used the tools, and could spread (b) (4) liquid on the (b) (4) unit. The peristaltic pump hose that is used to decant the (b) (4) after opening, prior to (b) (4) unloading, is placed haphazardly on the peristaltic pump, for the (b) (4) after each decanting unit operation. One operator knocked (b) (4) into the space between the (b) (4) bowl and housing. The operators perform this unit operation without a batch record or SOP. This (b) (4) has experienced high bioburden during non routine sampling for stability, see Observation 6 B, OOT investigation BA-OOT/22/004 26/04/2022.

B. While reviewing the Dynamic Smoke Study videos [ID 1013, 1014 and 1025] for (b) (4) (b) (4) purification operations, including (b) (4) (b) (4) we noted the following deficiencies:

   1. The operators did not exercise adequate aseptic techniques to protect the exposed (b) (4) DS intermediates and (b) (4) DS from potential contamination from the operators.
   2. Air was observed flow over the upper body of the operator into the open (b) (4)

C. While reviewing the recorded video of the (b) (4) unloading operation for (b) (4) for the ROW market, DS Batch # (b) (4) manufactured on 25/08/2022, in the inspection meeting

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room, we noted that the operators did not exercise adequate aseptic techniques to protect the exposed (b) (4) DS from potential contamination from the operators.

D. Collection of the (b) (4) are performed in the open in the (b) (4) grade C (b) (4) purification facility. (b) (4) are collected from a tube from the (b) (4) and transferred manually from collection (b) (4) to (b) (4) in the open. The area, as noted in C, above, is inadequately cleaned and maintained. There appears to be no EM performed during the (b) (4) collection procedure to verify open collection appropriateness.

E. (b) (4) for multiple (b) (4) purification steps are manufactured in open, uncontrolled environments. I.e., (b) (4)

F. You utilize (b) (4) µm filters (b) (4) (b) (4) Filter integrity testing (FIT) is only assessed after the (b) (4) step. Your FIT testing of the purification process (b) (4) µm filters is not adequately justified, and does not support product quality.

OBSERVATION 3

Supervisory oversight over the laboratory and manufacturing systems, including the electronic systems and data is deficient.

The list of observations noted in this form document that the Quality Unit has not performed the necessary assessments/reviews to ensure that the objectionable conditions do not negatively affect the manufacturing process and Quality Control tests in support of finished drug substances. Specifically,

A. Appropriate review of computers or related systems are not performed to assure that all changes in production records have been adequately documented and investigated. Your firm's Quality and Production units do not follow SOP S1/BA/QA/SOP/0044 titled "Audit Trail or Event Log Review Procedure", established since 06/19/2020, which reads in part "GMP data generated by manufacturing equipment's need to be reviewed during/after (b) (4) batch as applicable to ensure the operations are performed in validated/controlled state and integrity of the data is assured". Approximately one week prior to the start of the inspection, your firm discovered that this procedure has not been followed since inception in June of 2020, in that out of at least approximately (b) (4) (b) (4) upstream and downstream equipment which generate electronic data, only data generated by two (2) (b) (4) have been reviewed historically. Your firm issued a change control and

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identified all equipment to be reviewed going forward approximately one week prior to the start of the current inspection. Furthermore, our review of batch report event logs of your DCS-SCADA PCS equipment, with Wonderware software, for these (b) (4) used for (b) (4) operations for (b) (4) drug substance, found too numerous to list duplicated batch event report operations, unnamed batch operations, and "trial" batch operations. Our review of your batch event record audit trail found that your firm's review of the electronic data for the (b) (4) was inadequate, in that these discrepancies were not observed to be documented and/or investigated in your production batch records and review checklists. For example, per your firm, "trial" batches were manufactured by engineering and maintenance personnel for troubleshooting, however these activities were not always adequately documented by your Quality Unit. There is no assurance that electronic data such as, but not limited to, critical and non-critical alarms related to process, operator login and logout times, step change overs for (b) (4) recipe, and operator privileges generated by upstream and downstream production equipment during manufacturing operations is accurate, complete, and reliable with respect to official reported batch records.

B. During our review of your Empower 3 chromatography software, interrupted sequences were observed, which generated "Data Incomplete" chromatographic data. Your firm documented these interrupted injections as laboratory incidents, showing that no chromatogram had been generated, however, 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. As a result, during review of such cases, the interrupted sample injections were not adequately documented to be performed in your laboratory incident reports. Additionally, your firm has not demonstrated to understand the different types of communication errors and circumstances which may lead to a "Data incomplete" 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.

C. Approximately one week prior to the start of the inspection, your firm discovered that SOP S1/BA/QA/SOP/0044 titled "Audit Trail or Event Log Review Procedure" for electronic data generated by production equipment has not been followed since inception in June of 2020. Your firm issued a change control and identified all equipment to be reviewed going forward approximately one week prior to the start of the current inspection, however, your firm did not issue a deviation as required by your firms SOP C/GB/QA/SOP/0042 titled "Management of Quality Events", effective date 02/16/2022. Your firm initiated draft deviation 82981, dated 08/23/2022 after we discussed this discrepancy during the current inspection.

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D. 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.

E. The Quality Assurance Unit lacks adequate control over the issuance of laboratory worksheets such as your firm's "miscellaneous data sheet" and "reagent solution preparation details" used during testing operation in support of laboratory incidents, data invalidations, OOS investigations, and complain investigations. For Example, your firm uses a logbook to document the issuance of controlled perforated blank worksheets, however, does not have a procedure to perform reconciliation for the actual usage of these worksheets by QC personnel in the Quality Control laboratory.

OBSERVATION 4

Written procedures describing the handling of complaints do not include the provisions for review by the quality unit of any complaint involving the possible discrepancy with the drug product and a determination as to the need for an investigation.

Specifically,

Your firm has recorded one complaint in the last 2 years across all product codes with respect to drug substance (b) (4) dated 09/08/2021, with customer complaint no. 42602 described as "did not dissolve properly during manufacturing, this leads to blockage of the filter and low assay of the filtrate". As part of an initial investigation, the observation made by the customer was confirmed and your firm proceeded to continue the investigation at laboratory and manufacturing scale to find the root cause, with potential root cause identified to be associated with the longer filtration time of (b) (4) EP during the (b) (4) for (b) (4) preparation. Your firm identified this as a standalone complaint; however, during our review of your firm's quality unit operations, we observed similar concerns by other customers detailed as "During formulation of (b) (4) filter clogging issue observed" (customer query no BA/CQ/20/02, dated 11/12/2020) and "during filtration of formulation for batch (b) (4) filtration issue was observed by customer" (customer query no BA/CQ/21/01). Customer queries are detailed in SOP C/GB/QA/SOP/0005, titled "Handling of Customer Queries", effective date 05/02/2022, where queries are received by your firm's marketing and sales team, who are then required to pass down to Quality Assurance for determination if a query should be classified as a complaint.

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Your firm's handling of customer communication regarding issues with drug substance is not adequate, in that what appeared to be valid customer complaints, like complaint no. 42602, appeared to have been incorrectly classified as queries and not adequately investigated. All three customer complaints appeared to be similar in nature, where there may have been issues with drug substance solubility, potentially due to longer filtration time in the (b) (4) EP manufacturing process. As a result of different classification of customer communication regarding issues with products, there is no assurance that your firm can adequately trend and review your drug substance quality parameters for various Critical Quality Attributes (CQA)s and/or if a test method is suitable.

OBSERVATION 5

Your firm has not established scientifically sound and appropriate testing methods designed to assure that in-process materials conform to appropriate standards of identity, strength, quality and purity.

Specifically,

There is lack of assurance that the (b) (4) fermentation culture contamination check is able to recover contaminating microorganisms. During a facility walkthrough inspection, we observed your operators (b) (4) the fermenter sample port until the metal (b) (4) which could harm organisms in the fermenter sample. Contamination check plates were observed to have cracked during the PPQ runs deviations 36869, 38680, 38680, 39871. No data have been provided to demonstrate that the contamination check test is able to recover contaminating microorganisms in the presence of the host cell organism.

OBSERVATION 6

Your firm failed to ensure your investigations identify appropriate root causes, assess potential product impact, and implement sustainable corrective action and preventive action.

Specifically,

A Your deviation investigation 39041 12/8/2021 describes the clogging of the (b) (4) (b) (4) filters for (b) (4) k fermentation batches (b) (4) and (b) (4) The root cause for the clogging of the (b) (4) filters was determined to be a lot of (b) (4) raw material (lot (b) (4) that was delivered to the firm in drums, instead of in tanker trucks. The (b) (4) (b) (4) manufactured with the drum derived (b) (4) was visually a different color as compared to the firm's normal (b) (4) solution. The incoming drum derived (b) (4) passed the incoming raw materials testing for appearance. The Firm did not determine the contaminating components in

the drum derived (b) (4) or perform a risk assessment regarding these potential contaminants and their potential impact on (b) (4) drug substance quality. These DS lots, (b) (4) and (b) (4) were released 11-02-2022 and 10-05-2022, respectively. Your incoming raw materials specification for (b) (4) is not consistent with the USP monograph, including a lower purity for (b) (4) purity, non-volatile matter, and no testing for readily carbonizable and oxidizable substances.

B. Your OOT investigation, BA-OOT/22/004 26/04/2022, into the root cause of batch (b) (4) (b) (4) hold time study bioburden OOT of (b) (4) CFU/10 mL at 6 months, and (b) (4) CFU/10mL at 9 months, is inadequate. Bioburden recovered from the 9 month time point of your (b) (4) hold time study include *F.tularensis, S.paucimobilis,* and *A.lwoffii.* The (b) (4) hold time study was intended to support the (b) (4) expiry date of the frozen (b) (4) DS intermediate. You concluded that the there was no potential impact on process and process, as the samples tested were only for the hold time study. The (b) (4) intermediate (b) (4) was processed into (b) (4) (b) (4) DS batch (b) (4) and released on 25/02/2022.

OBSERVATION 7

There is lack of assurance that incoming raw materials testing used for the (b) (4) DS manufacturing is appropriately tested prior to use.

Specifically,

A. You utilize (b) (4) a critical product contact raw material, as a (b) (4) purification solvent. Your (b) (4) is recycled from previous product purification runs. (b) (4) recovered from (b) (4) processes are tested (QC/Q18B/SPEC/RM/116, version 003) and released for use in the (b) (4) steps for (b) (4) DS on Site (b) (4) (QC/Q18B/SPEC/RM/116, version 003). There is no assurance that the sole (b) (4) purity test method by GC can detect and quantitate all potential organic and/or inorganic impurities that may arise from the used (b) (4) and the recovering process.

B. Your incoming raw materials specification for (b) (4) does not meet the USP monograph for (b) (4) Deviation 39041 describes a visibly discolored batch of (b) (4) that was utilized for (b) (4) k fermentation batches (b) (4) and (b) (4) which you concluded in your investigation, caused (b) (4) filter clogging for those batches, which then required multiple unplanned interventions.

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C. Your incoming raw materials specifications for (b) (4) a critical raw material that is incorporated into the (b) (4) OS (b) (4) structure, is inadequate. Your in-house raw materials testing for (b) (4) has no specifications for identity or purity.

D. You have inadequate justifications or risk assessments for the use of raw materials not meeting USP monographs.

OBSERVATION 8

Your firm failed to provide adequate assurance that your cleaning procedures are effective to prevent cross-contamination for shared product-contact process equipment in the (b) (4) facility.

Specifically,

A. During the walkthrough inspection of the cell (b) (4) area on August 22, 2022, we observed white residue on the inside of view port window of a (b) (4) K Tank (SFP-PE-203) and the lid was partially closed. This multi-product equipment is labeled as "CLEANED AND READY FOR USE".

B. You failed to include surface swab sampling and testing in the fermentation and cell (b) (4) equipment cleaning validation study (BC/SFP/CV/R/008) that are used to establish the equipment dirty-hold-time.

C. Your manual cleaning procedure (S1/BA/PI/SOP/0090) does not provide adequate instructions to ensure that the cleaning of product-contact equipment used for (b) (4) process can be performed by your operators consistently. Importantly, the (b) (4) rinse volumes are not specified in the SOP.

OBSERVATION 9

Your firm has not established adequate procedural controls to protect the electronic data acquisition and/or systems used for (b) (4) drug substance manufacturing on Biocon Site (b) (4) manufacturing control

Specifically,

A. The computerized system (BRIAN CHILD; Model PR-20, SL.NO 159230018), used to collect data during the (b) (4) validation, has not been validated to protect original electronic records and

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relevant metadata (e.g., audit trails). During data review, only final printouts of the test results are reviewed, and they are not verified against the original electronic records.

B. 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" chromatographic data. Your firm has not demonstrated to understand the different types of communication errors and circumstances which may lead to a "Data incomplete" chromatography.

C. Your staff uses a common user name and password to access the SevenExcellence pH/Cond meter (Equipment ID. PHI-PHM-1183) used for the pH and conductivity measurements in the (b) (4) area of Building (b) (4)

OBSERVATION 10

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

Specifically,

A. Your control of your (b) (4) grade water, which is used for (b) (4) DS (b) (4) (b) (4) s inadequate. Your (b) (4) water does not meet the USP requirement for (b) (4) water for nitrates, ions and hydrocarbons. (b) (4) water is also utilized as the (b) (4) (b) (4) Your risk assessment evaluating the appropriateness of the use of the (b) (4) water in your GMP (b) (4) DS manufacturing process is inadequate (BP/TR/BL.15.0021/19/007). In addition, appropriate specification limits for Conductivity and TOC have not been established for the (b) (4) Treated Water" that is used for the (b) (4) processes.

B. Your control of your "Process (b) (4), which is used in the (b) (4) systems for fermenters and fermentation media is inadequate. Specifically,

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1. The "Process (b) (4) delivered to the facility has not been sampled at the points of use and tested for critical physical qualities (b) (4).
2. The specification limits of Conductivity and Total Organic Carbon (TOC) "Process (b) (4) (b) (4) (b) (4) µS/cm and (b) (4) ppm, respectively) are significantly higher than these specified in your (b) (4) Water (b) (4) µS/cm and (b) (4) ppb, respectively).
3. Chemicals, (b) (4) (b) (4) (b) (4) are added to (b) (4) feedwater to your "Process (b) (4) generation system. There is no documented quality assessment regarding the risks associated with the introduction of potential contaminants from the additives into your process. The vendors' certificates of analysis for the additives, which are accepted by your firm for raw material release, do not include any purity or impurity test.

OBSERVATION 11

Your firm's quality unit's oversight of your GMP manufacturing operations is inadequate.

Specifically,

A. Your firm lacks security control to prevent the access of GMP utility and equipment by the unauthorized persons on the campus. The following areas are not locked or have access control procedures in place to protect critical GMP areas and utilities:

- Building U4, (b) (4) KL Source Water Sump.
- Building U2, (b) (4) Treated Water Plant.
- Building U1, Central Utility Office, DG Room, (b) (4) Room, (b) (4) House, (b) (4) Room and (b) (4) Plant.

B. There is no quality agreement between your firm and Biocon Limited (FEI# (b) (4) who supplies (b) (4) treated water, process (b) (4) source water, (b) (4) water, and (b) (4) to your (b) (4) drug substance manufacturing facility.