DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
CDER/DBM, Attn: Zhihao (Peter) Qiu, Ph.D, Division Director 10903 New Hampshire Avenue; White Oak Building 22, Room 5112, Silver Spring, MD 20993 Phone: (301) 796-6655, Email: OPFBLAInspection483Responses@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	09/13/2021 - 09/24/2021
	FEI NUMBER 3011248248

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mr. Kiran Kumar Gandhirajan, Vice President and Site Head

FIRM NAME	STREET ADDRESS
Biocon Sdn. Bhd. (930330-U)	No.1, Jalan Bioteknologi 1, Kawasan Perindustrian SiLC
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
79200 Iskandar Puteri, Johor, Malaysia	Drug Substance and Drug Product Manufacturer

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

Observation 1:

(b) (4) is generated from (b) (4) with the (b) (4) distributed by (b) (4) to the drug substance facility. The (b) (4) is used in the (b) (4) process for the (b) (4) that includes (b) (4) into the vessels, along with (b) (4) (b) (4) and is used in further manufacturing that includes (b) (4) of the (b) (4) vessel and (b) (4) in support of product (b) (4) (non-marketed) and (b) (4) (b) (4) manufacturing. (b) (4) batches of (b) (4) (b) (4) U/ml (b) (4) (b) (4) (b) (4) mL) and (b) (4) batches of (b) (4) (b) (4) U/mL vial (b) (4) ml) have been distributed to the United States. The (b) (4) and distribution system is not qualified/validated nor is the (b) (4) tested for quality.

Observation 2:

Aseptic behavior and monitoring is not adequate. On September 17, 2021, during the manufacture of (b) (4) (b) (4) drug product (batch (b) (4) on Filler (b) (4) the following items were observed:

a. The Restrictive Access Barrier (RAB) (b) (4) that were (b) (4) Grade B space (b) (4) environmental monitoring plates, were not sanitized prior to (b) (4) Grade A space.

b. The described process in 2.a. is conducted (b) (4) during the filling operations that can be up to (b) (4) (b) (4) to include (b) (4) RAB (b) (4) interventions for such operation. The design of the environmental monitoring (EM) process for the filling machine is inadequate to minimize the number of RAB (b) (4) interventions, which may impact product quality during the manufacture of (b) (4) (b) (4) drug product.

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	Wayne Seifert Yetao Jin	Wayne Seifert, Consumer Safety Officer Yetao Jin, Chemist	09/24/2021

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c. During the exchange of EM plates, the technician sanitized their gloves for each entry into the filler's Grade A space, with environmental monitoring of the technician's gloves by finger dab performed after the last entry. Personnel environmental monitoring is only representative of that last EM plate change based on the design of the activities.

Observation 3:

According to document No. (b) (4) (b) (4) v3, (b) (4) for drug product manufacture (b) (4) is tested (b) (4) lot received. (b) (4) identification testing should be performed for each lot/shipment received, with the current procedure for frequency of test inadequate.

Observation 4:

Facilities and equipment are not adequately validated and maintained for (b) (4) manufacture. Specifically,

a. The (b) (4) product contact surface materials of construction are (b) (4) (b) (4) On 13 September 2021 as observed through the (b) (4) of the (b) (4) discoloration (black in appearance) was observed on the sidewalls of the vessels. The firm indicated the discoloration was rouge, with the qualified state not maintained.

Furthermore, within (b) (4) area, (b) (4) tank (b) (4) was observed with a line of discoloration on the interior vessel side wall. The firm indicated that this was under investigation and the potential root cause was an obstructed (b) (4)

b. Within (b) (4) (Grade D area) and near (b) (4) (Grade A air supply) for drug substance intermediate (b) (4) manufacture and dispensing, the wall mounted transfer lines (b) (4) with a (b) (4) (b) (4) covering were observed with the outer surface as dirty, uncleaned.

c. Raw materials are stored at 20 - 25°C in the Warehouse (b) (4) Store pending manufacture post (b) (4) This area is not validated for 20 - 25°C raw material storage.

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d. A floor seam within (b) (4) was observed in a deteriorated condition.

e. A (b) (4) leak was observed at (b) (4) on Equipment/FL (b) (4) for a (b) (4) drain line. The firm indicated that the leak was due to a faulty (b) (4) with no work order in place at the time of the noted observation.

f. (b) (4) was observed with a (b) (4) leak. You indicated the source of the leak was from the (b) (4) respectively. There was no work order in place at the time of the noted observation.

Furthermore, a (b) (4) leak was observed at the (b) (4). The firm indicated that the source of the leak was a loose (b) (4) with no work order in place at the time of the noted observation.

Observation 5:

Cleaning validations in support of (b) (4) drug substance manufacture are deficient. Specifically,

Cleaning validation excludes swab sampling of (b) (4) tanks, (b) (4) and chromatography skids. The firm indicates that (b) (4) testing mitigates the need for swabbing, where (b) (4) testing assures (b) (4) in support of effective cleaning. Though (b) (4) testing may assure adequate (b) (4) it should not be used as a substitute for not performing swabbing of equipment surfaces that may present an elevated challenge in removal of product residue. Furthermore, cleaning rinsate samples should include bioburden and endotoxin testing to a specification where (b) (4) are used.

Observation 6:

Standard operating procedure is inadequate. Specifically,

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According to trend reports for the (b) (4) used in drug substance manufacture (b) (4) (b) (4) (July 2020 - October 2020) and (b) (4) October 2020 - December 2020), pH was at an alert limit, generating a negative trend from approximately July 2020 to November 2020. Standard operating procedure (b) (4) (b) (4) v24, 6.12.2.e indicates if any physiochemical result exceeds the action limit for (b) (4) times for a sample point, an out of trend investigation will be initiated as per Handling of Out of Trend Investigations SOP, (b) (4) The procedure fails to elevate repeated alert level excursions that should include a trend investigation in mitigation of an aberrant condition and documentation of corrective action.

N/A sent 09/24/2021

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