DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Mahesh Ramanadham, PhD Director (Actg), Division of Inspectional Assessment, OPF/OPQ/CDER WO 51 RM 4238, 10903 New Hampshire Ave., Silver Spring, MD 20993 Phone: (+1) 301-796-3272 Industry Information: www.fda.gov/oc/industry	April 23 to May 1, 2018
	FEI NUMBER 3003981475

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mr. Shreehas P. Tambe, Chief Operating Officer

FIRM NAME	STREET ADDRESS
Biocon Limited	Special Economic Zone, Plot No. 2-5, Phase IV
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Bommasandra-Jigani Link Road, Bangalore, Karnataka, India	Drug Substance and Drug Product Manufacturing Facility

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

OBSERVATION 1

Disinfection efficacy is incomplete or not adequately demonstrated, specifically:

A. (b) (4) Efficacy study BF/STY/001/P (effective 14NOV2017) using sporicidal disinfectant completed for the (b) (4) Filling and Finish Area did not demonstrate effectiveness in controlling potential microbial contamination showing a minimum (b) (4)-log bioburden reduction. In addition, after (b) (4) an (b) (4) level of less than (b) (4) ppm residual of (b) (4) was not confirmed.

B. In Disinfection efficacy study performed per protocol BF/QCQ8/STY/P/313 the disinfectants were applied by spraying a thin layer of disinfectant directly on to coupons, and waiting for the specified residence times of (b) (4) (b) (4) before the efficacy log reduction was demonstrated. However, to clean production areas the disinfectant agent is applied using mops for ceilings, walls and floors and sprayed on lint free cloth and wiped on equipment.

OBSERVATION 2

Environmental monitoring is deficient. Specifically,

Microbial environmental monitoring is not conducted for open operations conducted for (b) (4) drug product formulation (b) (4) preparation, compounding and (b) (4) in (b) (4) -LAF-026 located in the formulation room (b) (4) (Grade C).

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	Laura Fontan Laurie Nelson	Laura Fontan, Consumer Safety Officer Laurie Nelson, Consumer Safety Officer	05/01/2018

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OBSERVATION 3

Cleaning procedures are inadequate, specifically:

During the observation of manual glassware cleaning in Grade D washroom F072 all product contact surfaces were not exposed to the cleaning agent ((b) (4) . Glassware was not filled to the (b) (4) as stated in procedure BF/FM/SOP/019 version 4. Cleaning of the glassware lids were not included in the cleaning procedure and were not exposed to the cleaning agent.

OBSERVATION 4

Inadequate behaviors to prevent contamination of raw materials were observed during the dispensing of raw materials for (b) (4) formulation (b) (4) specifically:

A. Dispensing operator cleaned the floor in front of the balances inside the hood with a (b) (4) sprayed wipe and did not change gloves or sanitize gloves before resuming dispensing activities.
B. Raw material containers were not wiped down with any sanitizing agent prior to entering dispensing hood.
C. After weighing, balance was cleaned with a (b) (4) wipe and then the same wipe was used to clean the table surrounding the balance.
D. The raw material (b) (4) was inside material entry/exit (b) (4) , stored inside a battered cardboard box inside a (b) (4) bag, (b) (4) bag and inner (b) (4) bag. The material was taken out of the cardboard box and placed inside a (b) (4) bin before entering the dispensing booth. This material specification contains (b) (4) and endotoxin limits.

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OBSERVATION 5

Operating procedure for dispensing of (b) (4) for manufacturing purposes does not reflect Quality Control sampling procedure for the routine monitoring of the (b) (4) system. Specifically,

SOP CQCM/SOP/007 version 4.0 states to open the sample valve (b) (4) and let the (b) (4) flow for (b) (4) and then (b) (4) the (b) (4) low to permit filling of the sample flasks/bottles. Procedure BF/FM/SOP/070, Operation of (b) (4) of Mobile Tank (b) (4) Fill Finish, version 4.0 does not require any (b) (4) dispensing (b) (4) into the tank.

OBSERVATION 6

Inadequate Trending analysis to identify potential issues that could impact product quality. Specifically:

A. Temperature controlled warehouse storage area WH033 which stores raw materials used in the (b) (4) formulation (b) (4) had temperature excursions above 25°C on April 18, 19 and 20, 2018. The temperature control range is 18 to 25°C.
-April 18, intermittent excursions above 25°C, with the longest period 15:56 to 18:46 (2 hours 50 min) with a maximum temperature of 25.3°C
-April 19, excursions above 25°C were from 15:26 to 19:26 (4 hours) with a maximum temperature of 25.3°C
-April 20, excursions above 25°C were from 14:26 to 18:46 (4 hours 20 min) with a maximum temperature of 26.1°C
No analysis for potential impact to materials stored in the warehouse was performed for these temperature excursions.

B. The (b) (4) trend review of microbiological and chemical analysis data for (b) (4) (b) (4) to (b) (4) does not include analysis of any bacterial endotoxin data.

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C. (b) (4) trend summaries for Environmental Bioburden Monitoring or (b) (4) Fill Finish, Trend for Out of Specification for (b) (4) and (b) (4) Formulations for (b) (4) to (b) (4) and Corrective Action Preventative Action Overview for the period (b) (4) to (b) (4) do not trend for root cause.

OBSERVATION 7

Inadequate equipment qualification/verification based on the documents provided. Specifically,

A. Cleaning verification executed per BF/QA/STY/P/105, effective 21SEP 2015 for direct product contact parts did not include glassware lids, which are potentially product contact. In addition, retrospective verification of personnel involvement in the manual cleaning procedure from July 2017 was provided. No documentation was provided to show that personnel were trained in the manual cleaning procedure prior to protocol execution.

B. Operational Qualification ETPL_EQDF_SI-810-004_V0.1, effective 23May2017, of balance (Equipment ID: W20-WB-07) did not include correct functional verification of the final package product weight check ranges using green light (acceptable) or red light (not acceptable) functionality.

C. There is no data to support that the (b) (4) line is sufficiently (b) (4) to remove other residual (b) (4) syringe filling. The (b) (4) (b) (4) and (b) (4) share the same supply line for the syringe filler.

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