DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Derek Smith, Ph.D., Division Director, U.S. Food & Drug Administration CDER/OPQ/OPF/DIA, 10903 New Hampshire Avenue, Building 51, Rm. 3171 Silver Spring, Maryland 20903 Derek.Smith@fda.hhs.gov 240-402-9091 Industry Information: www.fda.gov/oc/industry	February 7-8, 11-15, 2019
	FEI NUMBER 3003981475

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Srinivasan Raman, Senior Vice President & Global Head - Drug Product Operations

FIRM NAME	STREET ADDRESS
Biocon Limited	Plot No. 2, 3, 4, & 5, Bommasandre Jigani Link Road
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Bangalore 560 099 India	Drug Product Manufacturer

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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, written, adequately validated and/or followed. Specifically, you do not always have or follow appropriate written procedures designed to prevent microbial contamination regarding good aseptic techniques in the Grade A/B areas of your (b) (4) Manufacturing Drug Product Fill Line. The following are observations from the (b) (4) Fill Line operations on February 8, 11, and 14, 2019.

a) Operators do not perform inspection of the RABS(b) (4) after installation. Your written procedures "Operation and Cleaning of (b) (4) Testing Machine – (b) (4) Fill Finish," SOP BF/FM/SOP/182, v. 04, effective date January 8, 2019, p. 6 of 17, Section 6.1.iii., states "After fixing the (b) (4) to (b) (4) after the assembling and at the end of filling, visually inspect the (b) (4) throughout the (b) (4) between the (b) (4) for any obvious rips or integrity breaches or any damage, " and "Aseptic Behaviors in the Aseptic Processing Area and Periodic Review," SOP BF/FM/SOP/180, v. 07, effective date October 15, 2018, p.5 of 13, Section 6.7(k), states "(b) (4) should be visually inspected for any obvious rips or integrity breeches at the end of setup and after completion of the filling activity." Additionally, RABS(b) (4) are not checked pre-use and post-use when used thoughout fill operations.

b) An Operator in the Grade C area outside the Grade A/ISO5 Filling Line Capping and (b) (4) Section did not sanitize the RABS (b) (4) after an open-(b) (4) operation. Your written procedures "Aseptic Behaviors in the Aseptic Processing Area and Periodic Review," SOP BF/FM/SOP/180, v. 07, effective date October 15, 2018, p.5 of 13, Section 6.7(e), states "The filling machine shall be sanitized after each open (b) (4) operation during set up," and "Handling of Aseptic Interventions (Vial – Liquid/(b) (4)) –(b) (4) fill Finish," SOP BF/FM/SOP/194, v. 04, effective date December 12, 2018, p. 3 of 73, Section 6.1(h), states "After carrying out any open (b) (4) interventions…Wipe the inner surface of the (b) (4) with (b) (4) µ filtered (b) (4) /ready to use (b) (4) using lint free cloth or sterile pre–wetted wipes."

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c) Your written procedure, "Aseptic Behaviors in the Aseptic Processing Area and Periodic Review," SOP BF/FM/SOP/180, v. 07, effective date October 15, 2018, is inadequate. For example, Section 6.5 entitled "Aseptic behavior during assembling of filling machine/machine set up" does not provide instructions to prevent activities that could increase the introduction of contaminates into the Class 100 (ISO 5) when transferring large equipment from the lower (b) (4) shelf of the (b) (4) laminar air flow (LAF) (b) (4) Notably, on February 8, 2019 an employee in the Grade A/B was observed squatting down to retrieve an (b) (4) wrapped dosing vessel from the bottom shelf of the (b) (4) LAF (b) (4) and then placing the vessel into the open RABS. Additionally, Operators use clean room tables that have a top surface at knee height when performing operations, rather than surfaces at or above their ~~waste~~ Waste, during operations in Grade B areas.

d) Your written procedure "Microbiological Monitoring of Controlled Environment for (b) (4) Fill Finish," SOP BF/QC/SOP/148, V. 04, effective date February 6, 2019, is inadequate for environmental sampling. For example, an employee was observed squatting down to retrieve an (b) (4) dosing vessel from the bottom shelf of the (b) (4) LAF (b) (4) and then placing the (b) (4) wrapped vessel into the open RABS. After the dosing vessel was installed, assembly included removal of the aseptic covers from the vessel exit port and manifold bracket in the same location were the (b) (4) wrapped vessel was placed in the RABS. There is no environmental testing at the location where the dosing vessel is placed into the RABS or during the open aseptic connection between the vessel and the manifold.

e) Your written procedure "Approach for Aseptic Process Simulation," SOP BF/QA/SOP/002, V. 12, effective date June 30, 2018, is inadequate. For example, after media fill completion the units are transferred to the visual inspection facility after which all integral units are transferred to Quality Control Microbiology for incubation. The procedure states in Section 6.19 that the time gap between end of sealing and commencement of incubation should not be more than (b) (4); however, during the ≤ (b) (4) timeline there is no temperature criteria or secure location to store the units in the visual inspection facility.

f) The Visual Inspection of Vials, (b) (4) SOP is inadequate. For example, section 6.3 entitled Procedure for Manual Inspection does not provide adequate instructions on rejected vial tracking. Notably on February 12, 2018 an employee was observed removing a rejected vial from a vial (b) (4) placing it into a plastic bag and then into a small metal compartment under the viewing inspection table. The vial (b) (4) was then removed, and further processed for reconciliation. The rejected vial was placed in the bag with no (b) (4) or visual inspector

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identification. The (b) (4) supervisor stated the visual inspection employee was supposed to raise her hand to signal a rejected vial was recovered so he could document the vial (b) (4) and her identification on the bench sheet. When the employee opened her drawer to show the supervisor the rejected vial I noted several vials in the drawer without proper documentation on the supervisor's bench sheet. The Visual Inspection SOP states that rejected units should be kept separately in a plastic pouch with proper status label but does not describe adequate tracking criteria.

g) Sterile forceps stored in their RABS holders only allow for 2-3 inches of their sterile end to be accessible for handling when using the RABS(b) (4).

h) Operators place the sterile(b) (4) face down so that the dispensing nozzle is in direct contact with work surfaces in Grade B area.

OBSERVATION 2:
Written records of investigations into unexplained discrepancies do not always include an adequate conclusion and follow-up. For example, environmental monitoring excursion investigations and corrective actions over several months lacked effective CAPAs.

Summary Report for Trends for Environmental Monitoring Trend Review for Viable Environmental Monitoring Data of (b) (4) Fill Finish Facility for the Month of October included microbial recovery at location (b) (4) Grade A, (b) (4) The probably root cause and impact assessment stated that the microbiologist conducted swab testing by sitting inside the LAF and that the presence of the analyst under the LAF might increase chances of recovery. The Corrective Action included:

- No swab testing under the LAF and analysis shall be performed in a Biosafety cabinet
- The design of the LAF used for testing would be re looked at
- Training shall be provided concerning aseptic practices

The recovery of Micrococcus lutius (1 CFU/plate) on the (b) (4) was not considered a Significant Excursion.

Summary Report for Trends for Environmental Monitoring Trend Review for Viable Environmental Monitoring Data of (b) (4) Fill Finish Facility for the Month of November included but not limited to the following Grade A

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microbial recoveries;

- (b) (4) Near (b) (4), (8 CFU/plate)
- (b) (4) Near (b) (4), (1 CFU/plate)
- (b) (4) (2 CFU/plate)
- (b) (4) (1 CFU/plate)

The root cause investigation included:

- The microbiologist conducted swab testing by sitting inside the LAF and that the presence of the analyst under the LAF might increase chances of recovery
- Air sampling (b) (4) transfer and handling error
- Sampling error

Corrective Action included:

- No swab testing under the LAF and analysis shall be performed in a Biosafety cabinet
- The design of the LAF used for testing would be re looked at
- Training shall be provided concerning aseptic practices
- Dedicated (b) (4) per area
- (b) (4) imprinted with identification
- Initiate a change control to sterilize (b) (4) with the production load

It is noted that 25 excursions were identified in November 2018 in the Grade A vial Filling line.

Summary Report for Trends for Environmental Monitoring Trend Review for Viable Environmental Monitoring Data of (b) (4) Fill Finish Facility for the Month of December included but not limited to the following Grade A microbial recoveries;

- (b) (4) Near (b) (4) (1 CFU/plate)
- (b) (4) Near (b) (4) (18 CFU/plate)

The root cause investigation included:

- A potential broken lid on the (b) (4) sample plate and improper air sample (b) (4) handling
- Potential that transport bins were contaminated

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- Air sampling (b) (4) transfer and handling error

Corrective Action included:
- Training shall be provided concerning aseptic practices
- Evaluation on all interventions
- Dedicated (b) (4) per area
- (b) (4) imprinted with identification
- Change control initiated to validate sterilization of (b) (4) with the production load

It is noted that 26 excursions were identified in November 2018 in the Grade A vial Filling line.

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