DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER		DATE(S) OF INSPECTION
Office of Surveillance, Inspection Assessment Branch Food and Drug Administration-CDER/OC/DMPQ/ICT 10903 New Hampshire Avenue, Bldg 51, Room 4225 Silver Spring, MD 20993 Industry Information: www.fda.gov/oc/industry	Phone: 001-301-796-3334 Fax: 001-301-847-8738	5/25/2017 - 6/1/2017, 6/3/2017 FEI NUMBER 3003981475

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Arun Chandavakar, CEO and Managing Director

FIRM NAME	STREET ADDRESS
Biocon Llimited	Plot 2-4, Phase IV, Bommasasandra-Jigani Link Rd,Bommasandra
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Post Bangalore Karnataka 560099, India	Sterile drug 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 (I) (WE) OBSERVED:

Observation 1

Investigations of an unexplained discrepancy did not extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy.

A. Inadequate investigation into visible particulates observed in (b) (4) Injection, (b) (4) ng/ml. Since August 2015, the firm has observed particles in both long term and accelerated conditions. This material continues to be sold in Uruguay, Russia and Dominican Republic and has a (b) (4)

B. No risk assessment has been performed after the following updates to determine how the previous versions of these documents affected product on the market:
   - BF/QC/SOP/003 Microbiological Monitoring for Controlled Environment for (b) (4) and QC Laboratory. This procedure was updated to include monitoring finger dabs (b) (4) set-up to grade A limits, dated 23 May 2017.
   - BF/QA/SOP/002 Aseptic Process Simulation Strategy, effective 24 May 2017 for the addition of the review of media fills.
   - QC/SOP/042 Data Handling Systems Management, dated 22 May 2017, changed from reviewed (b) (4) (b) (4) audit trail to reviewing (b) (4) audit trail.

Observation 2

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile do not include adequate validation of the sterilization process.

A. Aseptic personnel are not tracked. Currently personnel who pass gowning qualification are allowed into the aseptic area regardless of whether they participated in a media fill.

B. There are no requirements for qualifying personnel during media fills. Activities performed during a media fill are tracked on a media fill tracking sheet since April 2017. There are no requirements specified in BF/FM/STY/P/171 Protocol for Qualification of Operators for Filling Operation for what duties need to be performed by operators to qualify them during a media fill. Management stated they are currently gathering data on what activities the operators are performing and will be setting requirements in the future.

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C. Filling times are not tracked during media fills. Only the initial start and stop times are documents. This reported time includes shut down periods where the (b) (4) vials are (b) (4) from the line and personnel leave the room. Shut down times are not documented.

D. The (b) (4) test, used to analyze sterile gloves, has not been validated.

E. BF/EM/SOP/069 Procedure for HVAC Validation & Requalification of aseptic areas does not take into account microbial levels in the room.

Observation 3

Aseptic processing area are deficient regarding the system for monitoring environmental conditions.

A. Aseptic operators are held to grade B qualifications even though they work in grade A areas.

B. Only testing gloves for grade A specifications (b) (4) set-up of the filling areas. The rest of the personnel monitoring is held to B specifications (b) (4) set-up.

C. Not specifying locations for environmental monitoring. Various locations were noted for location (b) (4) during the review of videos and documentation.

D. BF/QC/SOP/003 Microbiological Monitoring of Controlled Environments for (b) (4) and QC Lab, v10, dated 23 May 2017, was not being followed for swab sampling. This was noted during a review of a video of vial filling and was confirmed by microbiological management.

E. Particle counter is located (b) (4) away from filling (b) (4) in the PFS syringe filling area.

Observation 4

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established, written and followed.

A. (b) (4) tank bioburden samples are taken (b) (4) The firm lacks scientific rationale for not taking and testing bioburden samples (b) (4) step.

B. The firm routinely performs (b) (4) or (b) (4) disinfection of the cleanroom facility. However, (b) (4) disinfectant validation was not conducted inside the intended cleanroom; rather, validation was conducted in the general microbiology and the water testing rooms. The firm lacks scientific justification to conclude the validated disinfection effectiveness can be extrapolated or can be achieved when (b) (4) is carried out in the cleanroom.

C. Cleanroom garments are kept and reused for a specified amount of time according to SOP MM/MC/ SOP/003. For example, garments used in the Grade B cleanroom areas are disposed of after (b) (4) of use

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and reuse. The firm does not track and reconcile cleanroom garments that are expired or are at the end of use. There are no documented disposal records to assure all expired cleanroom garments are removed from circulation.

D. (b) (4) media plates incubated at dual temperature condition are used to capture both bacterial and fungal contaminants on the (b) (4) plates in EM, PM, and bioburden samples. The firm's (b) (4) plate dual temperature validation study is inadequate in that during the validation, bacteria species and fungal species was tested separately. They are not being tested together as a mixture of both organisms on the (b) (4) plate to mimic the actual use conditions.

E. All interventions are not being documented during sterile filling. This was noted during the review of CCTV videos obtained during the sterile filling of (b) (4) and vials.

F. Not following BF/FM/SOP/007 Transfer of Dispensed Materials to Respective Areas during the aseptic filling of (b) (4) lot (b) (4) dated 23 May 2017.

G. BF/FM/SOP/180 Aseptic Behavior procedure, v03, dated 27 May 2017 was not being followed during the review of CCTV videos on the vial filling of (b) (4) batch (b) (4) and (b) (4) filling of (b) (4) lot (b) (4)

- Using the same (b) (4) cloth during the entire length of production.
- Banging on window in Grade A area.
- Touching of the (b) (4) filling machine currently not being used during vial filling.
- Picking up a (b) (4) cloth from the floor.

Observation 5

Laboratory records do not include complete data derived from all tests, examinations and assay necessary to assure compliance with established specifications and standards.

A. Electronic data from chromatographic analysis is not available prior to 2010. This affects the application data summited in support of (b) (4) [niection. (b) (4) ng/ml equivalent base (b) (4) nl) and the method validation in support of (b) (4) [njection (b) (4) mg/vial.

B. Not all laboratory data were recorded accordingly. On 05/25/2017 a FDA microbiologist observed the following,

a. The firm's microbiologist read the settling plate at location Vial Sealing Area Passive (b) (4) on 05/24/2017 and reported "0" CFU. A FDA microbiologist observed 1 CFU for the same plate.

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b. The firm's microbiologist read Grade B finger dabs of employee (b) (6) Left hand on 05/24/2017 and reported "0" CFU. A FDA microbiologist observed 1 CFU for the same plate.

c. The firm's microbiologist read Grade B finger dabs of employee (b) (6) Right hand on 05/24/2017 and reported "0" CFU. A FDA microbiologist observed 1 CFU for the same plate.

C. Aseptic filling operators are monitored upon (b) (4) the cleanroom facility. However, aseptic area (b) (4) and (b) (4) records and personnel monitoring (PM) plates collected cannot always be reconciled. On 05/25/2017, we reviewed logbook records from 05/20/2017 to 05/24/2017 and observed the following,

a. On 05/23/2017, aseptic operator (b) (6) without documented (b) (4) the vial filling area at (b) (4) hour, and was missing a set of (b) (4) personnel monitoring plates that were documented to have been collected on 05/23/2017.

b. On 05/22/2017 operators (b) (6) and (b) (6) and on 05/23/2017 operator (b) (6) with neither (b) (4) records nor (b) (4) records for the vial filling area had their PM plates collected and incubated.

c. On 05/20/2017 operators (b) (6) and (b) (6) on 05/22/2017 operators (b) (6) and (b) (6) and on 05/24/2017 operators (b) (6) and (b) (6) had documented (b) (4) the vial filling area but did not have documented (b) (4) records had their PM plates collected and incubated.

D. The audit trail could not be provided in a usable format for the data obtained from the (b) (4) Agilent - OpenLab HPLCs in laboratory Q8 and (b) (4) Agilent – OpenLab HPLCs in laboratory Q13.

E. Quality Unit signs as verifying the interventions performed during media fills. This activity is not performed contemporaneously. Instead, Quality watches filling activities for the duration of the (b) (4) from a window in an adjoining room. At the end of the (b) (4) Quality personnel enter the filling area and signs off on any interventions performed during the (b) (4) Management admitted the times and actual number of interventions performed is not verified.

F. Raw data from the leak testing of sterile gloves is not documented.

G. Due to the data provided to the QC analyst upon receipt, the description test required by the sterile glove specification cannot be performed. This test has been listed as "complies" for all gloves received.

H. Procedure for Usage of Technical Information Sheet procedure does not following for EM samples and signing that the EM collected during media fill (b) (4) were documented as "pass" even though the following investigations were initiated and had yet to be closed; BF/OOS-02/M/16/030, BF/OOT/16/054, BF/OOS-02/M/16/031, BF/OOS-02/M/16/029, BF/OOT/16/053.

Observation 6

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Procedures for the cleaning and maintenance of equipment are deficient regarding sufficient detail of the methods, equipment, and materials used in the cleaning and maintenance operation, and the methods of disassembly and reassembling equipment as necessary to assure proper cleaning and maintenance.

A. The disinfectant efficacy study for (b) (4) for the organism cladosporium oxysporum was inadequate due to conflicting results being reported and an erroneous conclusions being reported. The organism was found during an OOS investigation into failed EM results obtained during a media fill for filling of sterile syringes in August 2016. The firm delayed executing the study until February 2017. The investigation determined the current hold time of (b) (4) for (b) (4) is inadequate and a minimum of (b) (4) is needed, however the cleaning method has yet to be updated with this information.

B. Cleaning of the (b) (4) spray bottles used during sterile filling is not documented. According to COA the bottles can be (b) (4) times. These spray bottles are not being tracked and the number of times the bottles are (b) (4) is not documented.

C. BF/FM/SOP.091 Cleaning of Aseptic Area (b) (4) Fill Finish procedure is not being followed. This was observed during the review of video for vial filling of (b) (4) batch (b) (4) dated 24 May 2017, and watching cleaning during the inspection. For example, cleaning with one cloth for the majority of the cleaning, and not cleaning in a unidirectional manner.

D. The firm has not sufficiently established the efficacy of disinfectants used in the aseptic processing areas, specifically,

   a. (b) (4) are used to clean filling machine surfaces. However, only (b) (4) machine surface had been challenged using the above disinfectants. The firm lacks scientific rationale for not challenging other representative machine surfaces, such as (b) (4) machine (b) (4) (b) (4) conveyor belt (b) (4) and (b) (4) transport (b) (4) wheels.

   b. (b) (4) are used to disinfect cleanroom surfaces. However, only (b) (4) surfaces such as cleanroom floors had been challenged with the above disinfectants using standard microorganisms and environmental isolates. The firm lacks scientific rationale for not adequately challenge other manufacturing surfaces, such as (b) (4) panels (ceilings), glass (light fixture covers), and (b) (4) (wall panels).

Observation 7

The quality control unit lacks the responsibility and authority to approve and reject all components and drug

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products.

Specifically,

A. BR/QA/SOP/039 Vendor Qualification procedure, v02, dated 30 December 2016, is not being followed for the supplier of sterile gloves.

B. Glove specifications do not include evaluation of the outer packaging.

C. The sample size of sterile gloves it not statistically representative. The firm samples (b) (4) gloves from (b) (4) receiving, regardless of how many gloves are received. Receiving have varied from (b) (4) to (b) (4) pairs of gloves.

D. During the review of the SAP system, (b) (4) of (b) (4) Injection, (b) (4) mg/ml, lot (b) (4) was in unrestricted use. This lot expired in January 2017.

Observation 8

Employees engaged in the manufacture and processing of a drug product lack the training and experience required to perform their assigned functions.

A. Colony growth on environmental monitoring (EM) and personnel monitoring (PM) plates are not always enumerated correctly. The firm lacks documented training or qualification program for conducting colony enumeration. On 05/25/2017 a FDA microbiologist observed the following,

   a. The firm reported CFUs in 9 out of the total EM and PM plates read on 05/24/2017. A FDA microbiologist observed additional CFUs that were missed by the firm's microbiologist in 6 out of the same 9 plates. The observed additional CFUs were confirmed by the firm's management.

   b. The firm reported CFUs in 17 out of the total EM and PM plates read on 05/23/2017. A FDA microbiologist observed additional CFUs that were missed by the firm's microbiologist in 10 out of the same 17 plates. The observed additional CFUs were confirmed by the firm's management.

B. There is a lack of documented CGMP training for IT personnel engage in the manufacture and processing of drug products. For example, IT personnel with administrator rights to the firm's HPLC, GC, UV, and IR computer systems do not have documented CGMP trainings.

Observation 9

Laboratory controls do not include the establishment of scientifically sound and appropriate specifications and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality and purity.

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The firm's bacterial endotoxin test for the finished product is deficient.

A. Bacterial endotoxin test (BET) method for the finished product is deficient in that it fails to adjust for the Maximum Valid Dilution (MVD) of (b) (4) sample such that it can lead to false negative results. GAM: QC/GAM/030, version 003, "Bacterial Endotoxin Test" MVD calculation method is based on (b) (4) unit of finished product and does not accurately reflect the MVD for the (b) (4) of (b) (4) units of finished products used in validations as well as in the routine bacterial endotoxin testing.

B. Only the pH of the samples, not pH of the sample-lysate mixture is measured as per USP requirement.

Observation 10

Procedures describing in sufficient detail the controls employed for the issuance of labeling are not followed.

Procedure was not followed in the destruction of secondary packing material. Specifically, on 05/29/2017 during the labeling and packaging of (b) (4) Batch: (b) (4) rejected labels bearing batch code, manufacture date, and expiry date were found in an unsecured waste bin. SOP BF/FM/SOP/076, "Precautions For Packing", version 04 states rejected packing materials must be placed in labeled and closed containers with lock and key.

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The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or

2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgement, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."