DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
CDER Division of Inspectional Assessment; Attn. Mahesh Ramanadham, Director E-MAIL: Mahesh.Ramanadham@fda.hhs.gov; PHONE +1-301-796-3272 Mail address: 10903 New Hampshire Ave. White Oak Building 51, Room 4328 Silver Spring, MD-20993 Industry Information: www.fda.gov/oc/industry	March 27 to April 7, 2017
	FEI NUMBER 3003981475

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Arun Chandavarkar, Ph.D., CEO & Joint Managing Director, Corporate

FIRM NAME	STREET ADDRESS
Biocon Limited	Plot No 2-4, Phase IV, Bommasandra-Jigani Road
CITY, STATE AND ZIP CODE Bangalore, Karnataka 560099, India	TYPE OF ESTABLISHMENT INSPECTED Drug Substance and Drug Product Manufacturing Facility

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:

1. There are discrepancies between the information submitted in (b) (4) and the (b) (4) manufacturing process performed at Biocon Ltd. For example,
   a. In-process specifications document QC/Q8/SPEC/IP/064 lists (b) (4) tests at (b) (4) steps as "Report Value"; however, section 3.2.S.2.4 of (b) (4) includes the following routine (b) (4) in-process action limits:

   b. Batch manufacturing record BMR-F-F02-700000665 indicates that the formulated bulk may be stored at 2 to 8°C for up to (b) (4) or (b) (4) (b) (4) C for no more than (b) (4) however, the hold is not included in (b) (4)

   c. Criteria specified in (b) (4) (Section 3.2.S.2.2) as "acceptance criteria" are defined as "action limits," "limits," or undefined specifications in the batch manufacturing record for the (b) (4) drug substance. Specifically,
      i. BMR-F-P02-700000868 for the (b) (4) production bioreactor states "if the cell concentration is less than (b) (4) cells/ml or more than (b) (4) cells/ml take a deviation and continue"; however, the parameter has an acceptance criterion in (b) (4)
      ii. BMR-F-P02-700000868 states "if residual (b) (4) is less than (b) (4) take a deviation and continue"; however, the parameter has an acceptance criterion in (b) (4)
      iii. The hydrophobic interaction chromatography in-process control specifications for (b) (4) by size exclusion chromatography (SEC), CE-SDS non-reduced (nrCE-SDS) and CE-SDS reduced (rCE-SDS) are controlled as acceptance ranges in (b) (4) but are described as

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"limits" in the corresponding batch manufacturing record BMR-F-D04-700000873.

2. The Quality assurance unit has approved and implemented documents that do not assure appropriate production, testing, and deviation review and release of commercial material. Specifically,
   a. The procedures for batch record review and batch release allow release of drug substance batches with open deviations or out of specification (OOS) results and for release of drug product made from such drug substance.
      i. MM/QA/SOP/004 "Review of Batch Records, Analytical Report, Relevant Records, Approval of Batch Release and Generation of CoA" for drug substance states that "if the deviation/OOS does not have any impact on the product/batch based on the completed impact assessment, but pending closure due to some other reasons, then batch can be released with appropriate justification" (Section 6.4.d). This is a "full" release, not a release under conditional quarantine status.
      ii. BF/QA/SOP/004 "Review of Batch Records, Analytical Report, Relevant Records, Approval of Batch Release and Generation of CoA" for drug product does not include a requirement to evaluate the deviation and OOS status of the drug substance used for the drug product manufacturing.

   b. The procedure for approving the test results for in process samples and raw materials (BF/QC/SOP/029 "Testing and Approval/Rejection") allows the analyst performing the testing to also perform the review of the data and release the data to QA or make a raw material usage decision in SAP.
      i. For in process samples, Section 6.7.6 states that "after completion of analysis, results are entered in TI sheet/BMR sheet and signed by the analyst." Then, Section 6.7.7 states that "the TI/BMR sheet with meta data will be reviewed and released with signature and date (signature can be either self or by a second analyst)."
      ii. For raw materials, Section 6.1.9 states "once the analysis is completed by analyst, results review and usage decision in SAP can be done from the same personnel whenever applicable."

3. Handling of in-process samples is inadequate. Specifically,
   a. Samples for (b) (4) detection using the culture/indicator cell method consist of the unprocessed

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bull(b) (4) BF/QC/SOP/080 "Sample Handling and Outsourcing to Contract Testing Laboratory".

b. Unprocessed bulk bioburden samples are settled for up to(b) (4) prior to testing. The samples are not mixed prior to testing and the test is conducted with the(b) (4) above the settled(b) (4) cells.

c. There is no time limit between sampling in the manufacturing area and transfer of samples to the microbiology or analytical Quality Control laboratories.

4. There is a lack of Quality oversight in the review of procedures followed in the quality control testing of(b) (4) drug substance and drug product. Specifically,

a. Instructions in the method SOPs in the QC laboratory are insufficient and/or inaccurate to ensure adequate testing of in-process intermediates for(b) (4) drug substance. For example,

i. SOP QC/GAM/035 "Bioburden Testing" addresses the receipt of the samples in the microbiology laboratory. However the SOP does not include instructions on how to aliquot and/or prepare the samples prior to the test. The routine practice of aliquoting unprocessed bulk samples into a bottle and settling the cells prior to testing is not captured in the SOP.

ii. SOP QC/Q8/FOR/072/02 "Bacterial Endotoxin Test Report" does not allow for documentation of the volumes used in(b) (4) step dilutions during sample preparation. Therefore the calculations used to prepare(b) (4) step dilutions cannot be verified.

b. Instructions for the actions to be taken based on results from in-process testing are insufficient to ensure adequate processing of the(b) (4) drug product. Specifically, the following statement is listed in Section 4.7.1 of BMR/F/700000751/23L-30L/02: "If the in-process test results for individual bag is out of limit for(b) (4) and(b) (4) then follow the below mentioned plan." However, the plan that is described in Table 14, does not include(b) (4) In addition, the number of times the recommended action is allowed to be executed before deferring to the acceptance limit is not indicated.

c. SOPs QC/Q8/SPEC/FP/114-01 "Standard Testing Procedure" for drug substance release and QC/Q8/SPEC/FP/097-01 "Standard Testing Procedure" for drug product release do not provide assurance

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that the methods can be suitably performed in the Quality Control laboratories and that the methods will remain in a validated state. For example,

i. Manual integration of the data is required to be or may be performed for SEC, nrCE-SDS, rCE-SDS, and IEX chromatography (IEC). Clear instructions regarding how to perform manual integration and when manual data integration can or cannot be performed are not provided to ensure consistency.

ii. The protocols for SEC, nrCE-SDS, rCE-SDS, and IEC do not specify whether new or atypical peaks would be identified and documented or investigated.

iii. Reagents, consumables, and equipment that may be substituted with "equivalent" include the QPCR Master Mix for the host cell DNA assay, the SEC column, and the SEC and IEC HPLC systems. The methods were validated for use with specific reagents and systems and it is not clear how the substitutes for the items specified in the methods are determined to be equivalent.

iv. The protocol for residual host cell DNA does not include key information to ensure appropriate DNA yield for testing. Ste[(b) (4)] includes an instruction to add water that has been "equilibrated to room temperature or at 70 degrees or more" and then to "incubate at room temperature or in a boiling water bath." However, to ensure an acceptable DNA yield, if the water is equilibrated at room temperature, the subsequent incubation must be performed in the boiling water bath, and if the water is equilibrated to 70 degrees, the subsequent incubation can be performed at room temperature.

5. The OOS procedure [BF/QA/SOP/029 "Out of Specification Procedure for Non-Conforming Materials and Drug Products (Analytical Tests)]" does not ensure satisfactory conformance to batch release specifications and appropriate investigation and tracking of OOS events, because it is internally inconsistent and not clear. Specifically,

   a. Section 6.1.a of the procedure indicates that OOS results from different test runs (different batches or products) performed on the same day may be reported under a single OOS.

   b. Section 6.9.B.b of the procedure states that retesting as part of a Phase II investigation is performed by[(b) (4)] analysts in triplicate; however, Annexure 8 used for conducting and documenting the investigation includes only two samples per analyst. Therefore, it is not clear whether samples are to be retested in duplicate or triplicate.

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c. Different and incomplete instructions for reporting retest results are included in Section B.f and Annexure-8.

6. (b) (4) and (b) (4) solutions used for drug substance formulation do not have adequate microbial control. Specifically,
   a. The (b) (4) solution is not tested for bioburden nor filtered prior to addition to the unformulated drug substance. In addition, the (b) (4) raw material has no vendor or in-house bioburden specification.
   b. The (b) (4) solution is not tested for bioburden nor filtered prior to addition to the unformulated drug substance. The (b) (4) raw material vendor specification is NMT (b) (4) CFU/g and in-house specification is total yeast and mold NMT (b) (4) CFU/g and total aerobic count NMT (b) (4) CFU/g; in-house specification bioburden levels would result in drug substance bulk bioburden of (b) (4) CFU/100 mL, which is (b) (4) fold higher than the proposed bioburden limit at this step.

7. Bioburden sampling during manufacturing of (b) (4) drug product is inadequate. Specifically, sampling of the (b) (4) used for drug product was performed immediately after the (b) (4) (b) (4) step.

8. Deviations are not initiated and/or closed in time, per the deviation SOP, and do not include appropriate justifications for delays in closure. Specifically,
   a. GB/QA/SOP/025 states that deviations should be closed within (b) (4) with a window period of (b) (4) In case of a delay in closure, the initiator is to enter the justification for the delay, and the delay is signed off for acceptance by QA. The following deviations were not closed or did not have delay approval within (b) (4) days:
      BL/DRU-15/007 due date: 15/06/2015 delay approval date: 03/08/2015
      BL/DRU-15/011 due date: 16/7/2015 delay approval date: 08/03/2017
      BL/DRU-15/037 due date: 09/10/2015 delay approval date: 04/27/2016
      BL/DRU-15/053 due date: 30/11/2015 delay approval date: 05/08/2016

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BL/DRU-15/062 due date: 19/11/2015 delay approval date: 09/12/2015
BL/DRU-15/063 due date: 17/11/2015 delay approval date: 05/08/2016
MM/DR-16/074 due date: 27/10/2016 delay approval date: 23/11/2016
MM/DR-16/160 due date: 26/12/2016 delay approval date: 16/01/2017
MM/DR-16/163 due date: 29/12/2016 delay approval date: 16/01/2017

b. GB/QA/SOP/025 states that deviations should be reported within (b) (4) from the time of the deviation. The SOP does not contain a differentiation between reporting and initiation of deviations. The following deviations were not initiated within (b) (4) of the "date of deviation" stated in the deviation report:

BL/DRU-15/062 date of deviation: 02/10/2015 date of initiation: 06/10/2015
MM/DR-16/029 date of deviation: 09/07/2016 date of initiation: 10/08/2016
MM/DR-16/097 date of deviation: 20/07/2016 date of initiation: 27/09/2016
MM/DR-16/160 date of deviation: 25/10/2016 date of initiation: 15/11/2016
MM/DR-16/168 date of deviation: 31/05/2016 date of initiation: 23/11/2016
MM/DR-16/199 date of deviation: 02/01/2017 date of initiation: 10/01/2017
MM/DR-16/202 date of deviation: 18/11/2016 date of initiation: 12/01/2017

c. In the event of a delay, a justification and target date are to be entered into the deviation report, the delay impact is to be assessed, and QA is to review and accept, if approvable. Many entries do not provide a suitable justification for the delay (more than 13 of the deviations reviewed during the inspection). A few examples for the delay include,

"prioritization of other activities"
"delay in CAPA initiation"
"delay in preparation of investigation report"
"discussion between cross-functional teams"

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