

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT OFFICE ADDRESS AND PHONE NUMBER Food and Drug Administration 10903 New Hampshire Avenue, Bldg 51, Rm 4225 Silver Spring, MD 20993 Phone: (301) 796-3334 Fax: (301) 847-8738 /E-mail CDEROSIAB@FDA.hhs.gov Industry Information: www.fda.gov/oc/industry	DATE(S) OF INSPECTION 6-15 February 2018
	FEI NUMBER 3011248248

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED
TO: Mr. Srinivasan Raman, VP Head Malaysia Operations

FIRM NAME Biocon Sdn Bhd	STREET ADDRESS No. 1 Jalan Bioteknologi 1, Kawasan Perindustrian SiLC
CITY, STATE AND ZIP CODE Iskandar Puteri, Johor 79200, Malaysia	TYPE OF ESTABLISHMENT INSPECTED 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:

PRODUCTION SYSTEM

OBSERVATION 1

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

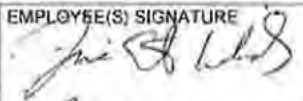

Specifically, your process simulation studies (media fill) are inadequate.

A. During my review of the media fill batch records (MFBR) for ^{(b) (4)} drug products (i.e. ^{(b) (4)} ^{(b) (4)}), I found that ^{(b) (4)} stoppered vials showing ^{(b) (4)} seal defect were rejected and not incubated.

For example,

- ^{(b) (4)} MFBR # ^{(b) (4)}, April 2016; 846 ^{(b) (4)} seal rejects
- ^{(b) (4)} MFBR # ^{(b) (4)}; May 2016; 2,007 ^{(b) (4)} seal rejects
- ^{(b) (4)} MFBR # ^{(b) (4)} May 2016; 1,310 ^{(b) (4)} seal rejects
- ^{(b) (4)} MFBR # ^{(b) (4)}; January 2016; 504 ^{(b) (4)} seal rejects
- ^{(b) (4)} MFBR # ^{(b) (4)}; January 2016; 139 ^{(b) (4)} seal rejects

According to control procedure BM/QA/SOP/019 "Aseptic Process Simulations (Media Fills) Section 6.1.5 states

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	EMPLOYEE(S) SIGNATURE 	EMPLOYEE(S) NAME AND TITLE (Print or Type) ROGER F. ZABINSKI, INVESTIGATOR	

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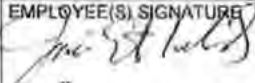

"Units with integrity defects (example: cracked units, broken units, container which are not sealed, vials without (b)(4) stoppers, etc.) shall not be considered as part of incubation and shall be reconciled and rejected accordingly. Therefore, your media fill practices and procedures are insufficient to justify excluding units in such circumstances. Even more, when the referenced drug products are multi dose products.

B. There is no assurance that your process simulation studies (media fills) performed in the (b)(4) Filling Machine (03-02-(b)(4)) are truly representative of the conditions observed and/or that might occur during routine aseptic filling operations of (b)(4). This is evidenced in that, although corrective and inherent operator's interventions are simulated during media fills, the frequency and the duration at which these interventions are simulated are not established based on a thorough evaluation of the historical and/or retrospective data.

C. The work conducted to re-qualify the (b)(4) Filling Machine (03-02-(b)(4)) used for filling solutions into (b)(4) and vials (Reports BM/PDP/RQ/P/050-02 & BM/PDP/RQ/P/041-01) respectively were found inadequate in that,

a. Your Quality Unit established the acceptance criteria for integrity, filling volume and seal integrity of the (b)(4) based only on the evaluation of the GOOD units post 100 % visual inspection. However, the approved re-qualification Report BM/PDP/RQ/P/050-02, dated 02/04/2018, does not include an evaluation of the rejected (b)(4) and the classification of the different defects found during the initial 100 % visual inspection. Moreover, there is no documented evidence that demonstrate the initial visual inspection was performed. Therefore, there is no assurance the results obtained during the re-qualification of the (b)(4) Filling Machine are accurate.

b. As part of the requalification activities of the (b)(4) Filling Machine (03-02-(b)(4)) for (b)(4) mL vial format, your Quality Unit requires the visual examination of (b)(4) vials for detecting the presence of integrity defects and contaminants in vials filled from (b)(4) % to (b)(4) % speed range. However, the approved requalification Report BM/PDP/RQ/P/041-01, dated 01/25/2017, does not describe the sampling plan that was followed and how was established the number of samples collected in order to ensure that representatives samples were taken for the visual examination.

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OBSERVATION 2

There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.

Specifically, there is a failure to consistently evaluate any unexplained discrepancy to ensure that (b) (4) drug products conform to the predetermined quality attributes.

Your visual inspectors have been rejecting in-process samples of (b) (4) drug products due to the presence of either integrity defects or foreign materials in aseptically filled (b) (4). Nonetheless, no manufacturing neither laboratory assessments have conducted even though the cause(s) that might be responsible for such conditions is not characterized.

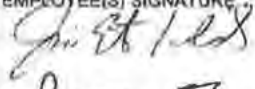

Your current practice is to conduct an investigation if the total number of (b) (4) rejected with defects during the manual inspection process is More Than (MT) (b) (4) %. This control limit applies to the different potential defects that could be detected in the manufacturing process of (b) (4) drug products, including (b) (4) particles, black particles, fiber, glass and broken (b) (4) among others. However, your current practice is indicative that you failed to consider other actions such as, technical analyses of the affected aseptically filled (b) (4) or a continuous monitoring of your process in order to identify through a scientific evaluation the potential source(s) and prevent re-occurrence.

QUALITY SYSTEM

OBSERVATION 3

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

Specifically, your firm uses common equipment and production processes for multiple drug products and drug substances such as (b) (4). Your Quality unit initiated more than

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1,040 deviations from 2015 to 2018, but has failed to extend the investigations of deviations (DR) and OOS discrepancies to other batches and products that were manufactured under similar conditions. This practice is indicative that you Quality unit failed to ensure the quality and production systems are in a state of control. The following deviations are examples of events where your quality unit did not extend the assessment of the investigation and to consider related root causes and to establish a CAPA in order to prevent adverse trends. In many cases the related product batch was released.

A. AQL Failures for Drug Product (DD/MM/YY)

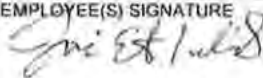

- | | |
|-----------------|------------|
| 1. BM/DR-17/037 | 04/05/2017 |
| 2. BM/DR-17/060 | 31/05/2017 |
| 3. BM/DR-17/066 | 06/06/2017 |
| 4. BM/DR-17/082 | 16/06/2017 |
| 5. BM/DR-17/120 | 28/07/2017 |
| 6. BM/DR-17/121 | 28/07/2017 |
| 7. BM/DR-17/152 | 16/08/2017 |

B. (b) (4) or (b) (4) OOS for Drug Substance

- | | |
|---------------------|------------|
| 1. BM/DR-17/196 | 10/03/2017 |
| 2. BM/DR-17/217 | 10/17/2017 |
| 3. BM/OOS-02/16/001 | 05/05/2016 |
| 4. BM/OOS-02/16/055 | 04/02/2017 |
| 5. BM/OOS-02/16/059 | 12/03/2017 |
| 6. BM/OOS-02/16/060 | 16/03/2017 |

C. OOS for (b) (4) for (b) (4) System Sampling (b) (4) or (b) (4) System)

- | | |
|-----------------|------------|
| 1. BM/DR-17/204 | 09/10/2017 |
| 2. BM/DR-17/244 | 31/10/2017 |
| 3. BM/DR-17/268 | 15/11/2017 |

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- | | |
|-----------------|------------|
| 4. BM/DR-17/290 | 23/11/2017 |
| 5. BM/DR-17/296 | 28/11/2017 |
| 6. BM/DR-17/307 | 04/12/2017 |
| 7. BM/DR-17/318 | 11/12/2017 |

OBSERVATION 4

Written production and process control procedures are not followed in the execution of production and process control functions.

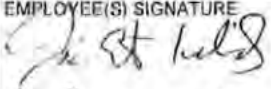

Specifically, your Quality unit has not always followed and executed your procedure for deviation management regarding drug product and drug substance. Your procedure BM/QA/SOP/024, version 004, titled "Deviation Management", effective 19 January 2018 states:

A. Section 6.2.4 note-1, that prior deviations of similar nature that occurred in the last ^{(b) (4)} are considered as recurring type;

B. Section 6.2.12(b), that all deviations shall be closed within ^{(b) (4)} days with a grace period of ^{(b) (4)} _{(b) (4)} days;

C. Section 6.2.13(a), that delays in deviation closure should be justified with a reason and a target completion date.

During the years 2016-2017, your firm had over 748 deviations with an average of 17% overdue past the target date and an average of 34% of recurring deviations, per the ^{(b) (4)} deviations trending reports.

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Date Range	Total Deviations	Open and Overdue Target Date	Percent Overdue (%)	Recurring	Percent Recurring (%)
(b) (4)	135	25	19%	54	40%
	104	13	13%	37	36%
	90	19	21%	37	41%
	88	9	10%	35	40%
	102	15	15%	16	16%
	71	20	28%	*ND	*ND

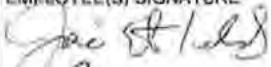

LABORATORY CONTROL SYSTEM

OBSERVATION 5

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

The work conducted to validate the cleaning process of non-dedicated manufacturing equipment (e.g. flexible hoses and (b) (4) sensor tip) located at Drug Product Plant under validation report (BM/PDP/CV/P/001-01) was found inadequate.

Specifically, the validation studies conducted to justify the cleaning acceptance criteria for (b) (4) with (b) (4) drug product failed to include the recovery studies for the different surface materials (e.g. (b) (4) and (b) (4) found in the manufacturing train of (b) (4) drug product. Therefore, there is no assurance the results obtained for the collected samples during subject validation activities are accurate.

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FACILITIES AND EQUIPMENT SYSTEM

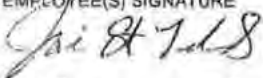
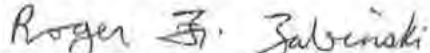
OBSERVATION 6

Procedures for the cleaning and maintenance of equipment are deficient regarding inspection of the equipment for cleanliness immediately before use.

Specifically,

A. Procedure # BM/EM/SOP/048-PM, version 004, titled "Visual Inspection Machine Preventive Maintenance Procedure", effective 31/10/2017 that is used for finished Drug Product automated visual inspection is deficient for the following reasons:

1. The light intensity (LUX) is not monitored or calibrated to ensure that the automated camera detection can be assured.
2. The procedure calls for ^{(b) (4)} cleaning and preventive maintenance. Your firm has not established if ^{(b) (4)} PM is adequate or if more frequent cleaning is needed depending on the equipment usage and number of batches produced. The procedure states that when dust is found it is to be ^{(b) (4)} away using a ^{(b) (4)} but the procedure does not define if the dust will be move to other parts of the machine. The procedure calls for cleaning and preventive maintenance to be completed by the engineering department, not by the equipment operators.
3. The procedure does not call for the tracking or trending of dirt, dust, debris, or malfunctions of the machine. For example, deviation BM/DR-17/120 on 28/07/2017 was for a failed AQL for batch ^{(b) (4)}. Your firm identified a possible root cause of broken ^{(b) (4)} and that the machine had not been cleaned before continuing the inspection of samples.

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