DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	
DISTRICT ADDRESS AND PHONE NUMBER 12420 Parklawn Drive, Room 2032 Rockville, MD 20857 ORAPHARMInternational483responses@fda.hhs.gov	DATE(S) OF INSPECTION 07/10/2023-07/20/2023 FEI NUMBER 3011248248
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED Mr. Kiran Kumar Gandhirajan, Senior Vice President & Site Head	
FIRM NAME Biocon Sdn. Bhd. (Company No. 201101002193)	STREET ADDRESS No. 1 Jalan Bioteknologi 1, Kawasan Perindustrian SiLC
CITY, STATE, ZIP CODE, COUNTRY 79200 Iskandar Puteri, Johor, Malaysia	TYPE ESTABLISHMENT INSPECTED 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 WE OBSERVED:

DRUG

OBSERVATION 1

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

(**This is a repeat observation**)

A. On 07/10/2023 and 07/12/2023, we inspected the post assembly and/ or aseptic filling of (b) (4) (b) (4) (b) (4) (b) (4) mL batches (b) (4) respectively. We observed the following deficiencies.

- Aseptic operators blocked HEPA unidirectional airflow when re-plenishing (b) (4) stoppers and (b) (4) seals to their respective (b) (4).
- Sterile scissors used to cut open (b) (4) bags containing sterile components were held in non-sterile holders when not in use.

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- Section of the (b) (4) that was exposed to the Grade B area was not (b) (4) (b) (4) before returning to its Grade A position.
- On 07/10/2023, the inner surfaces (Grade A side) of the RABS (b) (4) sectioning off the (b) (4) from the Grade B side were not sanitized after performing (b) (4) interventions.
- On 07/12/2023, the aseptic operator stood inside the Grade A area while cleaning the inner surfaces of the RABS (b) (4) after (b) (4) interventions.
- BM/PDP/SOP/140 lacks sufficient details on how to clean RABS (b) (4)
- Insufficient amount of (b) (4) was applied to the (b) (4) to clean RABS surfaces.

B. We watched videos of your firm's airflow visualization studies conducted in 06/2023 and observed the following.

- HEPA unidirectional airflow to the (b) (4) was blocked during replenishment of (b) (4) stoppers and (b) (4) seals.
- Aseptic operator's head, right shoulder and arm were seen inside the Grade A area during (b) (4) (b) (4)
- Aseptic operator's head, upper chest, both shoulders and arms were seen inside the Grade A area during (b) (4) seal (b) (4).
- Cleaning of the (b) (4) RABS (b) (4) after (b) (4) interventions was not simulated.
- (b) (4) sanitization during (b) (4) interventions were not simulated to assess risk of creating Grade A turbulent air by using (b) (4) bottles.
- Demonstration of (b) (4) sanitization with (b) (4) was different from the routine practice.

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C. According to your (b) (4) Production Manager (b) (6) and your Deputy Manager (b) (6), your firm does not conduct (b) (4) integrity testing to ensure that there are no microscopic defects such pinholes and tears that can sibly seen before use in aseptic production of your sterile injectable drug products. At least (b) (4) batches of sterile (b) (4) and (b) (4) batches of sterile vials were manufactured for distribution to the United States since January 2020 where (b) (4) integrity testing was not performed therefore, there is no sterility assurance that the (b) (4) are adequate for use prior to start of aseptic production.

OBSERVATION 2

There is a failure to thoroughly review the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed. Specifically,

On 03/20/2020, out-of-trend (OOT) result of (b) (4) % for (b) (4) Impurities ((b) (4) (limit. (b) (4) %) was reported for (b) (4) (b) (4) Origin) drug substance (DS) batch (b) (4) The above batch was placed on stability on (b) (4) but released on (b) (4) to make into drug product (DP) batches (b) (4) (placed on stability), (b) (4) which were dispatched to the U.S. market between 08/2020 and 01/2021.

However, on 11/06/2020, DS batch (b) (4) result of (b) (4) % (b) (4) failed 6-month long term stability. Your firm failed to test retention samples or place additional DP batches on stability after discovering the failure. Your stability failure investigation concluded that there was no product impact thus notification through Biological Product Deviation Report (BPDR) to the U.S. FDA was not

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necessary. Your sponsor (b) (4) reviewed and accepted your investigation and impact assessment. Based on the assessment, conformed that no BPDR was required to the U.S. FDA. However, your firm's investigation lacked adequate scientific justification for allowing all (b) (4) impacted (b) (4) DP batches to remain in the U.S. market unit expiry (b) (4)

OBSERVATION 3

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

A. Assigned root causes for laboratory OOS results are not always scientifically justified.

a) BM/OOS-02/20/015 was initiated on 12/01/2020 for OOS results observed in assay (potency) for (b) (4) injection (b) (4) (D) (4) IU/mL stability samples (b) (4) 2M LT and (b) (4) 2M accelerated. Your firm's investigation concluded that analyst error involving pipetting/dilution was the probable root cause. However, your investigation did not contain confirming information because the conclusion of analyst error was not supported by the Phase I investigation. Further, Hypothesis analysis was performed and the outcomes was also OOS. No phase II manufacturing investigation was conducted. A new composite sample was tested, the results were within acceptance and the original OOS results were invalidated. A common filling batch (b) (4) used to fill batch (b) (4) was also used to fill (b) (4) U.S. batches (b) (4) (Expiry (b) (4) . Impact to product quality would have been extended to the two U.S. batches had the original OOS results were not invalidated.

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b) BM/OOS-02/21/006 was initiated on 05/21/2021 for OOS results observed in assay (potency) for (b) (4) injection (b) (4) (b) (4) IU/mL (b) (4) stability samples (b) (4) 2M LT and (b) (4) 2M Phase I investigation noticed increase in area response. No hypothesis studies were performed. The above investigation concluded the OOS results were attributed to instrument breakdown. However, your firm's investigation did not contain confirming information in that the HPLC system suitability and standards were within specification and the conclusion of instrument malfunction was not substantiated by the instrument service vendor. No phase II manufacturing investigation was conducted. The observed OOS results were invalidated and the distributed batches (Expiry (b) (4) remained in multiple markets (b) (4) (b) (4) .

c) BM/OOS-02/22/034 was initiated on 12/22/2022 for impurity OOS result observed in (b) (4) (b) (4) for (b) (4) DS In-Process (IP) batch (b) (4) The result for (b) (4) Relative Retention Time (RRT) was (b) (4) % (limit. (b) (4) . Phase I investigation did not identify any laboratory errors. Re-measurement of the original samples concluded the OOS was due to transient malfunction of the instrument. However, the re-measurement activity was conducted without QA or QC approval. Based on the outcome of the re-measurement, re-test was performed and meeting acceptance. The original OOS was invalidated and (b) (4) DS batch (b) (4) was released on 02/08/2023 to (b) (4)

d) OOS investigation #BM/OOS-01/22/31 is inadequate in that you have not scientifically justified the root cause of the total organic carbon OOS found during sampling of point (b) (4) from (b) (4) which was collected on (b) (4) and found to be (b) (4) ppb whereas the specification for TOC is NMT (b) (4) ppb . You determined the that (b) (4) (b) (4) used for disinfectant solutions were the root cause of the TO e however, there is no evidence to

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support and justify that a (b) (4) containing disinfectant residue after (b) (4) is attributable to a higher TOC count.

B. Deviation investigations regarding post (b) (4) ntegrity failures are inadequate.

Specifically, your deviation investigations regarding post (b) (4) integrity failures (leaks and physical defects) found after completion of aseptic batches are inadequate because you failed to take into account that you do not perform (b) (4) integrity testing therefore, there is no way to determine whether the integrity leaks and/or physical defects found during the (b) (4) integrity testing performed (b) (4) were intact prior to start of aseptic operations or if (b) (4) breaches were caused during inherent/corrective interventions during aseptic production. For example,

- On 09/02/2020, (b) (4) not used in aseptic production failed the post integrity test of Manufacturing Batch (b) (4) (Deviation PRID #2926)
- On 07/27/2020, (b) (4) failed post integrity test after completion of Manufacturing Batch (b) (4) (Deviation PRID #1847)
- On 06/11/2021, (b) (4) failed post integrity test due to a tear found during (b) (4) verification after completion of Manufacturing Batch (b) (4) (Deviation PRID# 48749)
- On 08/26/2022, (b) (4) failed the post integrity test of Manufacturing Batch (b) (4) (Deviation PRID# 83542)

OBSERVATION 4

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Failure to have written procedures to describe in detail corrective/preventative actions during loss or reversals of different pressure of your classified aseptic areas.

Specifically, your firm has no written procedures on what corrective actions are to be performed when aseptic areas have a loss in differential pressure to return to a state of cleanliness that is suitable for resumption of aseptic operations. Your SOP entitled, "ENVIRONMENTAL MONITORING ON TEMPERATURE, RELATIVE HUMIDITY AND ROOM AIR PRESSURE DIFFERENTIAL IN CLEANROOM AREA", Document No. BM/PDP/SOP/018, Version 008, Effective 12/13/2022 is inadequate because it does not address how to mitigate nonviable/viable contamination after a loss/reversal in differential pressure that exceed your established limit of (b) (4) For example,

- Deviation PRID #3034- Loss of differential pressure for 47 minutes in the aseptic filling area during production of (b) (4) Batch (b) (4) on (b) (4) through (b) (4)
- Deviations PR #1322- Loss of differential pressure for 30 minutes in the aseptic filling area during production of (b) (4) Batch (b) (4) on 6/25/2020.
- Deviation #78215- Loss of differential pressure for (b) (4) in the aseptic filling area during (b) (4) Vial Batch (b) (4) on 07/20/2022.

Furthermore, your study conducted to establish differential pressure excursion specification limit of NMT than (b) (4) is inadequate because it was conducted at rest and does not demonstrate that classified aseptic areas will be in state of control during a loss/reversal of differential pressure during aseptic activities.

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OBSERVATION 5

Your firm fails to establish and document the accuracy, sensitivity, specificity, and reproducibility of its test methods.

Specifically, (b) (4) stoppers are being used for product contact container-closures for (b) (4) vial and (b) (4) However, your firm's (b) (4) for both vial stoppers and (b) (4) stoppers are deficient to assure product quality and patient safety.

A. The (b) (4) method for (b) (4) (b) (4) mL vial (b) (4) stoppers was validated at the Biocon Bangalore site and transferred to the Biocon Malaysia site. However, method transfer study was not performed per section 6.2 of the BM/QA/SOP/081, entitled " Procedure for Method Validation , Method Transfer and Method Verification", v 003 to demonstrate that your QC Laboratory has the procedural and technical ability to perform the transferred method as intended.

B. Your firm does not perform routine (b) (4) to qualify each incoming lot of (b) (4) stoppers. You rely on information provided in the supplier's Certificate of Analysis (COA). However upon further review, your supplier's COAs do not contain (b) (4) results information.

OBSERVATION 6

Employees engaged in the manufacturing and processing of a drug product lack the training required to perform their assigned functions. Specifically,

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There is a lack of (b) (4) refresher CGMP training for Process Research & Development personnel (a total of (b) (4) employees) who support the manufacturing of (b) (4) DS and DP for commercial distribution. Currently, personnel in the Process Research & Development Department receive initial onboard CGMP training but are not given (b) (4) efresher CGMP training.

DEVICE

OBSERVATION 7

Risk analysis is inadequate.

Specifically, (b) (4) RISK MANAGEMENT REPORT RMSR 0004-2015 Rev 01 dated August 10th 2015 up to the current Rev 06 dated July 29th, 2020 does not address the control of injection force on the (b) (4) finished product (b) (4) unit) for each individual lot release. In addition, there are no design inputs/ outputs or transfer activities identified for injection force testing for each individual lot release for (b) (4) finished product.

(b) (4) was released to the market in (b) (4) with (b) (4) lots ed to the US market for (b) (4) (lot sizes (b) (4) units). Injection force on the (b) (4) finished product was not conducted for any of these lots released to the U.S. market. Since the 2020 release to the U.S. market, there have been 1620 complaints received for (b) (4) which meant that no drug product could be administered. There have been multiple incidents that more than one (b) (4) failed to (b) (4) drug.

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OBSERVATION 8

Corrective and preventative action activities and/or results have not been adequately documented.

Specifically, CAPA # 95196 dated November 25th, 2022 was initiated to address (b) (4) ssues. Within this CAPA complaint samples from dated November 25th, 2022 to present have been tested for friction force on the (b) (4) However, injection force on the retention samples for these complaint lots were not tested. This CAPA is currently still open to investigate ongoing (b) (4) issues which are occurring in the field (Globally with the majority of issues seen in the U.S. market).

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