DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
FDA/CBER/ (b)(6) 10903 New Hampshire Avenue, Silver Spring, MD 20993 Attention: Telephone (b)(6) Industry Information: www.fda.gov/oc/industry	04/11/2022 to 04/19/2022
	FEI NUMBER 3020223359

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Dr. Umesh Shaligram, Executive Director, Serum Institute of India Pvt. LTD

FIRM NAME	STREET ADDRESS
Serum Institute of India Pvt. Ltd.	S. No. 105-110, majari Bk. Tal. Haveli
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Manjari Bk., Pune 412 307	Biological 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

Good Documentation Practices (GDP) and data integrity practices were deficient. Specifically,

a) Deviation Report No. M26/06/21/03, dated 6/19/2021, (b)(4) (b)(4), reported that the limit of conductivity for (b)(4) was documented as (b)(4) instead of (b)(4) in the following records: 1) Master Formula Record (MFR) for (b)(4) of (b)(4) 2) Batch Manufacturing Record (BMR) for (b)(4) and (b)(4) scale for Manufacturing of (b)(4) (BMR no. MBR/ (b)(4) and 3) SOP for Preparation of (b)(4) Area - & - of (b)(4) (SOP No. 1011-0073-000). A typographical error occurred while preparing the SOP, BMR, and MFR where a [ ] was typed instead of a [ ].

b) Deviation Report No. M03/07/21/01, (b)(4), reported on 7/3/2021, in the [ ] for GMP -- cleaning in the -- area, that "[ ]" was written on page no. - of -, after completion of cleaning on 6/30/2021, for the remaining entry lines. After the operator was accidentally hit by a --, page number - of - was inadvertently torn from the (b)(4), resulting in a damage (torn) (b)(4) page. The operator discarded the completed page due to panic and fear of being caught by the supervisor. GMP [ ] cleaning was performed on 6/30/2021, but the -- cleaning entry on 6/30/2021, which was documented on page -, was not available.

c) Deviation Report No. M19/07/21/01, dated 7/18/2021, (b)(4) (b)(4), noted during processing of Batch no. (b)(4) there was a typographical error in the Master Batch Record (MBR) for flow rate during continuous (b)(4) The flow rate was incorrectly documented as (b)(4) instead of (b)(4) during the drafting and typing of the MBR.

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d) Deviation Report No. M13/11/21/03, dated 11/12/2021, (b)(4) (b)(4), noted the following observations.

i) Batch (b)(4) - On page number - of -, multiple errors were committed during the (b)(4) calculation. The operator corrected the errors and signed on the original date of the calculation (9/1/2021) and not the later correction date. The same errors were also reflected on page - of - and page - of -.

ii) Batches (b)(4) and (b)(4) - On page number - of - of Batch (b)(4) & page no. - of - of Batch (b)(4), the (b)(4) was inadvertently made "NA" before completion of activity entries. Irrespective of the log being "NA", the operator signed the - sheet with the entry error.

e) Deviation Report No. M29/11/21/02, dated 11/29/2021, (b)(4) (b)(4), reported the (b)(4) Audit Trail was misplaced. The last audit trail of the - Bioreactor was performed on 11/22/2021, and the (b)(4) was found to be misplaced while performing the audit trail on 11/29/2021. The missing (b)(4) was never found.

In 2021, 131 of 416 Deviations were for Good Documentation Practice Error. Since January 1, 2022 to present, 23 of 400 Deviations were for Good Documentation Practice Error.

Observation #2

Deficiencies were observed in the detection of (b)(4) of the (b)(4) (b)(4) method:

a. No control is included in the initial (b)(4) step to ensure acceptable quality and quantity of DNA used for the subsequent (b)(4) reaction.

b. The instructions given for the interpretation of the test results shown in Table 1 of SOP # 1003-0393-002 are

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inaccurate/inapplicable. For example, the test is recorded as presence of the (b)(4) if the Ct value (b)(4) and the (b)(4) is Pass/Fail/Unused. However, if the (b)(4) is failed or unused, the test should be invalid because of the presence of potential (b)(4) substances. In addition, some scenarios listed in Table 1 indicated that the (b)(4) is not being used; however, the firm confirmed that the is always included in each assay run and thus they are not applicable to the current assay set up.

Observation #3

There is no data to demonstrate that the potency of the (b)(4) reference standard Lot # (b)(4) used for potency determination of - and DP has no significant change between the initial qualification performed in September 2021 and the re-qualification of the reference standard performed in January 2022.

Observation #4

batches of (b)(4) were manufactured with a process that is different from the - process submitted under the . Due to the leakage observed during the (b)(4) (Deviation M25/08/21/02), the (b)(4) was harvested by (b)(4) instead of the established process of (b)(4). However, there was no Process Performance Qualification data at Serum Institute to support using the (b)(4) to harvest the (b)(4) for the - process. The (b)(4) harvest batch (b)(4) was used to produce (b)(4) batches, and subsequently these batches were used to formulate - DP lots (b)(4) and - out of - DP lots were released. In addition, - of the - batches (b)(4) was used to validate the - process with a MOI of -.

Observation #5

There is inadequate data in the (b)(4) lifetime use validation study to support a comparable - performance in the binding capacity of the (b)(4) and removal of process impurities over the

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proposed lifetime of [redacted] for the (b)(4) and (b)(4)
(b)(4)

Observation #6

Reporting of deviations and investigations were deficient as follows:

a Inconsistent categorization of recurring deviations:

i. M11/01/22/04 was categorized as major deviation while M30/01/22/01 was categorized as a critical deviation with the same incident of media contamination due to [redacted] clogging.

ii. M23/08/21/01 and M15/01/22/01 were both categorized as major with the same incident of unusual peak observed in (b)(4).

b. SOP for the reporting of deviations does not have instruction on the upgrading of the severity of deviation if a similar incident reoccurs.

c. A [redacted] throughput study was performed to investigate the root cause of the clogged [redacted] in deviations M11/01/22/04 and M23/08/21/01. The outcome of the study suggested that the current [redacted] configuration is appropriate only for the (b)(4) and therefore (b)(4) are recommended ([redacted] the current number of [redacted] used) for the (b)(4) of (b)(4) used in the [redacted] step of the [redacted] bioreactor. The same (b)(4) study is also applicable to the [redacted] process because the same [redacted] is used for the (b)(4) used in the [redacted] step; however, the firm did not re-evaluate if an additional [redacted] may be needed in the (b)(4) to mitigate the potential contamination caused by the clogging of [redacted].

d. Deviation M23/08/21/01 was initiated because an unusual peak was observed during the (b)(4). The (b)(4) of the (b)(4) was substantially different from the (b)(4) of the [redacted] batches for the [redacted] process. According to the investigation, the root cause was the failure of [redacted] and [redacted] of the (b)(4). However, the firm did not perform any product impact assessment by

including additional characterization testing nor stability study for this affected batch. The firm only relied on the release batch results to justify product quality.

e. The investigation of Deviation M24/06/21/01 did not take place in a timely manner. The deviation was initiated on June 24, 2021, because the operator collected a sample from - batch (b)(4) through the (b)(4) with a (b)(4) instead of a sample (b)(4). The contaminant (b)(4) was possibly introduced in the (b)(4) bioreactor because of the incorrect sampling. The QA interview with the operator was not taken place till (b)(4) the occurrence of the deviation on July 26, 2021.

Observation #7

Written procedures for maintenance fail to include schedules for the replacement of HEPA filters prior to failure.

Observation #8

Equipment cleaning following preventive maintenance was not performed on the (b)(4) used in (b)(4) manufacturing. As a result, (b)(4) batch failed endotoxin testing.

Observation #9.

Corrective actions are not completed in timely manner. For example:

a) (b)(4) cycles were aborted three times due to low concentration of (b)(4). Preventive maintenance to be completed to (b)(4) after cleaning of (b)(4).

b) On 1/17/2022, leakage was observed in (b)(4) equipment during (b)(4) of (b)(4). This same (b)(4) was used for (b)(4). SOP (#1012-0054) to be revised to include instruction to perform leak test (b)(4) and preventive maintenance (PM) to be revised to include cleaning of (b)(4) PM. This action and other PM actions (cleaning of (b)(4) and vendor evaluation) are still pending at the time of this inspection.

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Observation #10

Aseptic processing areas are deficient regarding the system for monitoring environmental conditions. Specifically,

a) You do not perform [redacted] identification each time action level is reached for each [redacted] (b)(4) [redacted].
b) Your [redacted] did not consider manufacturing operations when determining sample locations.
c) You do not perform complete investigations when an action level is reached to include root cause and corrective action.
d) You do not have a system in place that allows for monitoring recurring [redacted] to identify repeated significant organism.

Observation #11

The initial [redacted] fill validation did not follow the protocol for the total number of interventions including the following:

- Transfer of sterile filling [redacted] into [redacted]
- Transfer of [redacted] (b)(4) into [redacted]
- Connection of [redacted] container to [redacted]
- Removal of [redacted] (b)(4) from [redacted]

(b)(6)

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DATE ISSUED
04/19/2022

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."