DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
60 Eighth Street NE Atlanta, GA 30309 (404)253-1161 Fax:(404)253-1202	11/19/2024-11/27/2024* FEI NUMBER 1039284

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Luis Bosques Crespo, Site Lead

FIRM NAME	STREET ADDRESS
Merck Teknika LLC	100 Rodolphe St Bldg 1300
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Durham, NC 27712-9402	Biological drug product 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:

OBSERVATION 1

The responsibilities and procedures applicable to the quality control unit are not fully followed.

Specifically,

A. The review and approval process of the qualification of major equipment is deficient. Requalification of the (b)(4) used in (b)(4) Suite, Room (b)(4), performed in March 2023, failed, which led to the initiation of a significant investigation, QN 201091153, on 03May2023.

The BCG Vaccine manufacturing process has two (2) Critical Process Parameters (CPP) associated with the (b)(4) and (b)(4). The (b)(4) is utilized to cool the (b)(4) (b)(4) prior to use during the (b)(4) Process.

A repeat requalification was performed on 9Jun2023 using the protocol (b)(4)-(b)(4). The associated investigation was closed on 15Jun2023, and equipment was released for manufacturing, without confirming that the generated data were within the acceptance criteria.

Quality review and approval of the executed re-qualification protocol was completed only on 08Nov2024. During the review process, the firm identified that the execution performed on 9Jun2023 failed due to (b)(4) data points reported outside the acceptance criteria of the protocol. The delay in Quality review process led to utilize the equipment in its failed requalified state

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since 9Jun2023.

B. Procedure SOP-6970/QC50.308, *Data Invalidation Procedure* (Version 7.0, Effective Date: JUL-11-2024) outlines steps required for identifying, assigning, and tracking invalid data generated by testing performed in the BCG (b)(4) laboratories. This procedure requires invalid data trending reports to be conducted on a (b)(4) basis. These reports require approval from QC Management and Quality. However, the reports REF-013935057, REF-014096931, REF-014354108, which covered the period JAN-01-2023 to DEC-31-2023, JAN-01-2024 to MAR-31-2024, and APR-01-2024 to JUN-30-2024 respectively, were approved by QC management only.

OBSERVATION 2

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

Specifically,
Airflow visualization studies (Smoke studies) were not performed for the following inherent and corrective interventions performed during the aseptic (b)(4) process of BCG Vaccine.

A. On 20Nov2024, during the fill line setup of BCG Vaccine batch (b)(4) using aseptic (b)(4) (b)(4), we observed a Grade (b)(4) operator using an empty tray for removing the entire vials from the vial (b)(4), as a vial storage (b)(4) was accidentally slipped and fell over the vials. This intervention was never evaluated in the air flow visualization studies.

B. The (b)(4) changeout is a corrective intervention during the (b)(4) process. This was never evaluated through smoke studies.

C. On 20Nov2024, during the (b)(4) set-up for BCG Vaccine batch (b)(4), the (b)(4) had alignment issues. The Grade (b)(4) operator entered inside the protective enclosure around the

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(b)(4) to complete the set-up process. This intervention was never evaluated in the air flow visualization studies. (b)(4) were present in the (b)(4) during this corrective intervention.

OBSERVATION 3

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

Specifically,
On 20Nov2024, during the (b)(4) process of BCG Vaccine batch (b)(4) using aseptic (b)(4), we observed the following:

A. Grade (b)(4) Operators involved in (b)(4) assembly set-up and (b)(4) operation lacked deliberate (b)(4)
B. During adjustment of (b)(4), the Grade (b)(4) operator's arms and upper torso were observed reaching over the (b)(4).
C. (b)(4) used for troubleshooting the non-viable particulate (b)(4) alarms were not discarded after touching the (b)(4). The (b)(4) was placed near other (b)(4) which were utilized by Grade (b)(4) operators for opening the (b)(4) of (b)(4).
D. (b)(4) inside the Grade (b)(4) operator's goggles was observed.

OBSERVATION 4

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

Specifically,
a. The firm has initiated about 9 deviation investigations pertaining to exceedance of "(b)(4) (b)(4)" defects (Critical defect). This is a critical defect with an action limit of NMT (b)(4) (NMT

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(b)(4) after January 2024). These deviations related to action level defects are still ongoing, despite corrective maintenance and CAPAs.

Notification Number	Batch	Product in (b)(4) defect %	Product Inspection / AQL Date	Root Cause
201023681	(b)(4)		25-Aug-22	(b)(4) misalignment: bulk of (b)(4) defects occurred prior to intervention to correct (b)(4)
201046528			2-Nov-22	(b)(4) misalignment during setup
201066792			30-Jan-23	(b)(4) sealing
201142692 (AQL failure)			13-Nov-23	Missed defect during product inspection
201140987			3-Nov-23	(b)(4) that is used to move vials was causing product in vials to (b)(4). (b)(4) was adjusted to slow it down.
201142875			3-Nov-23 10-Nov-23 21-Nov-23 7-Dec-23	(b)(4) malfunction: suspect (b)(4) were removed from process, the (b)(4) defect generation rate decreased significantly, indicating that the root cause of the (b)(4) defects was due to (b)(4) malfunction.
201187804			30-May-24 6-Jun-24	(b)(4) alignment due to setup variability
201192046			19-Jun-24	(b)(4) alignment due to setup variability
201220844			4-Oct-24 18-Oct-24 13-Nov-24	Ongoing investigation

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b. Deviation QN 201039748 (initiated 10/06/2022) for BCG Batch (b)(4) and QN 201189268 (initiated 06/09/2024) for BCG Batch (b)(4), were found out of specification (OOS). The BCG means for both batches were (b)(4) exceeding the release specification of (b)(4) per test method, (b)(4), *"Dry Weight Determination"*. According to (b)(4), *Test Investigation Procedure for Out of Specification (OOS) and Atypical Results,* a Data Validity Task ((b)(4) (b)(4)) should be created in (b)(4) as part of the (b)(4) analysis to determine whether the test is valid or invalid before conducting a retest. Despite this requirement, no data validity task was created in (b)(4); retests were performed on 01/30/2023 for Batch (b)(4) and on 08/26/2024 for Batch (b)(4). The initial test results generated on 10/06/2022 and 06/09/2024 were invalidated without quality approval prior to retesting.

Both BCG batches, (b)(4) and (b)(4), were subsequently released based on the retest results without properly determining the validity of the original test.

c. Your firm failed to initiate a deviation or exception report when the 2023 annual requalification, dated 09/25/2023 (b)(4) of the (b)(4), used to sterilize (b)(4).) and (b)(4), (b)(4) etc.) failed acceptance criteria deeming the run invalid. A second run cycle was performed 11/15/2023 which resulted in failure to meet acceptance criteria. The firm initiated a work order, WO 53653773, to inspect the door (b)(4) and it was observed that the (b)(4) door (b)(4) was replaced. A (b)(4) requalification run cycle was performed on 01/18/2024, which resulted in a failure to meet acceptance criteria. The root cause was determined to be a malfunctioning (b)(4); however, the (b)(4) was determined functioning prior to use, according to the (b)(4) temperature report, dated 09/13/2023. A (b)(4) requalification run cycle was performed on 02/07/2024. The firm's investigation initiated based on the (b)(4) run cycle failure did not include a risk assessment for the batches manufactured prior to the WO performed on 11/15/2023. There were (b)(4) of BCG batches manufactured and released using (b)(4) and (b)(4) sterilized in the (b)(4), from 09/25/2023-11/15/2023.

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OBSERVATION 5

Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design to facilitate operations for its intended use.

Specifically,
The (b)(4) used in (b)(4) Suite, Room (b)(4) is utilized to (b)(4) the (b)(4) for (b)(4). The firm's requalification performed in 9Jun2023 using the protocol (b)(4) was designed to study the criteria for (b)(4), while in production, the time allowed is a (b)(4). The requalification strategy is not designed for the (b)(4) to ensure that the (b)(4) are cooled to (b)(4) of (b)(4).

The firm manufactures about (b)(4) BCG vaccine batches (b)(4) utilizing this equipment.

OBSERVATION 6

Equipment and utensils are not maintained at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product.

Specifically,
From 03/31 to 04/07/2023, during annual requalification of the (b)(4) ((b)(4)), the equipment underwent maintenance to replace and (b)(4) (b)(4) used during production. However, (b)(4) (b)(4) remained in service throughout this period. Sterilized components from the (b)(4) were used in the manufacture and release of (b)(4) BCG batches for distribution.

***DATES OF INSPECTION**

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11/19/2024(Tue), 11/20/2024(Wed), 11/21/2024(Thu), 11/22/2024(Fri), 11/25/2024(Mon), 11/26/2024(Tue), 11/27/2024(Wed)

X Lizaida Perez
Investigator
Signed By: 2004213019
Date Signed: 11-27-2024 11:32:46

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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 judgment, 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."