DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
CBER/OCBQ/Division of Manufacturing and Product Quality 10903 New Hampshire Avenue, Silver Spring, MD 20993 Lead Insp.: Holly Brevig Telephone: 301-796-0742 Industry Information: www.fda.gov/oc/industry	November 4-12, 2024
	FEI NUMBER 3001314775

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Carsten Schneider, Marburg Site Head and Managing Director

FIRM NAME	STREET ADDRESS
GSK Vaccines GmbH	Emil-Von-Behring-Str. 7
CITY, STATE AND ZIP CODE Marburg, Hassia, 35041 Germany	TYPE OF ESTABLISHMENT INSPECTED Vaccine Bulk Product

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. Maintenance of facilities and equipment used in the manufacture of biologics are deficient.

a. The facility and equipment used in the manufacture of Shingrix (Building (b) (4) are deficiently maintained to ensure the quality of the bulk drug substance. On November 4, 2024, November 5, and November 11, 2024, the following conditions were observed:

i. A (b) (4) liquid was observed to be leaking from (b) (4) in Room (b) (4) which is a (b) (4) used for product (b) (4) (b) (4)

ii. (b) (4) residues were observed on the (b) (4) which is used in downstream manufacturing of Shingrix and contained in Room (b) (4). This (b) (4) shows accumulation of (b) (4) residues suggestive of material egress from the (b) (4). This (b) (4) is a (b) (4) drug substance, (b) (4)

iii. (b) (4) residues were observed on the (b) (4) used in downstream manufacturing of Shingrix (Room (b) (4)). The (b) (4) displayed (b) (4) discoloration. (b) (4) (b) (4) displayed a (b) (4) hue. (b) (4) there was an accumulation of a (b) (4) liquid.

iv. (b) (4) residues were observed on the (b) (4) (b) (4) in Room (b) (4) which is used for clean-in-place (CIP) and steam-in-place (SIP) of the (b) (4)

v. (b) (4) residue was observed between (b) (4)

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in Room (b) (4) which is used for (b) (4) (b) (4) Further, (b) (4) streaking was observed below the (b) (4) residue.

vi. (b) (4) residues were observed on (b) (4) used to (b) (4) (b) (4) in Room (b) (4)

vii. (b) (4) residue was observed on the (b) (4) that is used to transfer media from (b) (4) respectively, in Room (b) (4)

viii. (b) (4) remnants were observed on a (b) (4) attached to (b) (4) ir Room (b) (4)

ix. (b) (4) residues were observed on the (b) (4) used to (b) (4) (b) (4) in Room (b) (4) utilized for downstream purification.

Since October 2022, 11 deviations associated with equipment leaking or dripping vessels or equipment in the same manufacturing area have been reported.

Since the last preventive maintenance of the area, (b)(4) drug substance lots have been manufactured. A product impact analysis of the (b)(4) drug substance lots and a retrospective analysis of previous lots manufactured have not been performed.

b. The facility and equipment used in the manufacture of Measles bulk drug substance (Building (b) (4)) are not maintained in a good state of repair. Specifically,

i. On November 07, 2024, deterioration of (b) (4) was observed in the classified areas used to manufacture Measles bulk drug substance. Specifically, in Grade (b)(4) areas (including Room (b) (4) the (b) (4) were visible due to the deteriorated (b) (4)

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ii. On November 08, 2024, damage to a (b) (4) used to (b) (4) was observed behind the peeling (b) (4) used for patching in classified Room (b) (4)

iii. The speed of the (b) (4) is not monitored during routine production or verified on a routine basis.

2. Critical utilities (b) (4) utilized as product (b) (4) in the manufacture of Shingrix are not adequately qualified or routinely monitored to ensure reproducible quality. Specifically, (b) (4) quality control testing is not performed on the (b) (4) received (b) (4) and a routine monitoring program has not been established for these utilities that are supplied throughout the facility (b) (4) Further, the utilization of these (b) (4) has continued in the absence of completed qualifications of the (b) (4) (b) (4)

3. Quality oversight and integrity of electronic data captured to support the manufacturing equipment, environmental monitoring, and manufacturing systems (e.g., Process Control System) has not been established. For example:

a. For the (b) (4) assessments:

i. Electronic documentation of the (b) (4) of the (b) (4) performed on May 8, 2024 is missing.

ii. Self-tests for internal diagnostics of equipment were aborted or failed on October 29, 2024, and June 17, 2024, respectively, without explanation or documentation.

iii. (b) (4) which is used for the (b) (4) instruments, lacks a requirement for quality oversight of the associated testing and metadata.

b. For the (b) (4) procedure 9000087546 titled SDOC - Environmental Monitoring, version 04 permits measurements to be interrupted [aborted] and repeated immediately for occurrences such as

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(b) (4)

These interruptions are not subject to documented quality oversight. Aborted testing was observed in the (b) (4) electronic audit trail. For example, particulate measurements of the classified areas used to manufacture Shingrix were aborted without contemporaneous quality review, and there is no record of an investigation, trending, or reporting the events aside from the audit trail (e.g., June 19, 2024, May 23, 2024, August 08, 2024).

c. For the Process Control System (PCS) for the manufacture of Shingrix, critical alarms termed (b) (4) are to be the subject of a documented investigation per SOP 9000056671 titled Alarm Management, version 16. A review of the PCS demonstrated the occurrence of (b) (4) alarms that have not been investigated as mandated per the SOP. For example, deviations were not opened when different operators on March 22, 2024 and July 24, 2024 did not correctly (b) (4) system following planned maintenance, which resulted in an upper limit (b) (4) measurement and (b) (4) upper alarm limit.

4. Deviation management is inadequate to demonstrate quality oversight of the manufacturing process, and does not adequately identify, document, or investigate the impact to drug substances. For example:

a. Procedure 9000075940-02, MZP: Alarm Management and Audit Trail defines critical (b) (4) alarms (defined as (b) (4) as (b) (4) critical, (b) (4) Since October 09, 2024, there have been (b) (4) critical (b) (4) alarms that are (b) (4) critical. Despite these (b) (4) critical alarms, (b) (4) has not reviewed, evaluated, or otherwise acknowledged these alarms since October 09, 2024 (as of November 09, 2024). Without (b) (4) of these alarms, the production department continues to issue batch records for the manufacture of Shingrix drug substance per SOP 9000080766 version 4 titled eBR Execution and Review and has initiated manufacture of (b) (4) batches of Shingrix drug substance without the evaluation of these (b) (4) of alarms.

b. High bioburden levels were discovered during a lifetime study of (b) (4) (b) (4) has a (b) (4) which was identified as a source of bioburden contamination to the Shingrix drug substance. Manufacture of Shingrix drug substance continues at risk with (b) (4) (b) (4) Correction of the equipment design is not scheduled until March 2025.

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5. There is inadequate quality oversight to assure that the Shringrix and Measles drug substances have the identity, strength, quality, and purity they purport or are represented to possess. For example:

a. High bioburden levels were discovered during a lifetime study of (b) (4) (b) (4) Quality assurance invalidated this data during the lifetime study, albeit the data was considered valid data by quality control.

b. There is no quality oversight of unplanned maintenance events to assess the qualification/validation status and product impact. Specifically, procedure GUI-9000055892-24 General Procedure of Preventive and Corrective Maintenance does not require the quality unit's approval for any unplanned maintenance or repairs to the facility.

c. Documentation practices are insufficient. For example, (b) (4) (b) (4) in classified Room (b) (4) used to manufacture Measles bulk drug substance lacked supporting documentation.

d. Signed and dated original documents pertaining to the (b) (4) of materials used in the manufacture of Measles drug substance were found in the trash.

6. There is a lack of data to demonstrate the quality of the (b) (4) prior to use for vaccine production. (b) (4) the (b) (4) have not been inspected and documented for (b) (4) before use for the upstream manufacturing process.

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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 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."