

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION					
DISTRICT ADDRESS AND PHONE NUMBER 10903 New Hampshire Ave, Bldg71, Rm 5054 Silver Spring, MD 20993-0002 (240) 402-9160 orabioinspectionalcorrespondence@fda.hhs.gov		DATE(S) OF INSPECTION 1/8/2024-1/26/2024* FEI NUMBER 3006738517			
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED Andrea D'Amato, Site Director					
FIRM NAME GlaxoSmithKline Vaccines Srl		STREET ADDRESS Localita Bellaria			
CITY, STATE, ZIP CODE, COUNTRY Sovicille, Rosia, 53018 Italy		TYPE ESTABLISHMENT INSPECTED Vaccine 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 There is a failure to thoroughly review any unexplained discrepancy and 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, the following was observed: a) Covering the time period of January 2021, to the present, invalid test rates for release testing assays pertaining to Menveo and Bexsero drug substance (DS) and drug product (DP) batches were observed to routinely exceed the firm's QC trending investigation threshold of (b)(4). Within 2023, multiple assays were observed to have invalid rates exceeding (b)(4). During review of 2023 data, it was observed that CAPAs were only opened for Menveo (DS & DP) and Bexsero (DS) (b)(4) assay (3 CAPAs and Menveo (DS) and Bexsero (DS) (b)(4) assay (1 CAPA). Invalid rates were observed as high as (b)(4) for (b)(4) and (b)(4) assay. It was observed that no CAPAs were initiated to implement corrective action and prevent future occurrence of (b)(4) trending excursions for the following assays observed at over (b)(4) invalid rate during (b)(4) analysis (this list is not all inclusive). • Menveo (DS & DP) - (b)(4) on conjugated bulks (b)(4) (b)(4)					
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- Menveo - (b)(4) in (b)(4) (DP) and (b)(4) (DS) (b)(4) - Bexsero (DS) - (b)(4) on (b)(4) (b)(4) - Bexsero (DS) - (b)(4) (b)(4) - Bexsero (DS) - (b)(4) (b)(4) b) While reviewing Shingrix complaint investigations (all presentations), it was observed that complaint trend excursion investigations for stopper coring complaints were conducted in (b)(4) due to increased reports of coring complaints (b)(4). Results of both investigations concluded there were no quality issues identified and no corrective actions were implemented. During the (b)(4) investigation, it was identified that the most probable root cause for the complaint increase was due to the usage of needle sizes with larger borings (outside of the 21 - 25G range utilized during clinical trials) by health care providers. Shingrix labeling and prescribing information does not indicate what size of needle to be utilized during administration. Since					
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2021, approximately 189 coring complaints have been received from ROW and U.S. markets equating to approximately 30% of total received complaints for Shingrix during that time period. To date, no corrective actions have been implemented to reduce the frequency of coring complaints received from the market.			
OBSERVATION 2 The responsibilities and procedures applicable to the quality control unit are not fully followed. ,Specifically, the following was observed: a) The firm reported over 5500 deviations between January 2021 through December 2023. For 2023, root causes were classified as: [redacted] method, [redacted] machine, and [redacted] manpower (human error). The firm does not assign most deviations as recurrences due to a reported limited definition in [redacted]. The firm has not performed analysis of the deviations per related topics, similar root cause, manufacturing production unit, or product to determine if there are clusters of similar deviations that may be recurrences and if there may need to be a general or master deviation or master CAPA to address these similar events. A review of the deviations revealed clusters of deviations under similar topics: [redacted] for equipment; [redacted] for HEPA and other filter failures; [redacted] for water, [redacted] (b)(4) [redacted] for training; [redacted] interventions (including [redacted] (b)(4) maintenance [redacted] (b)(4) interventions). The firm has not established CAPA effectiveness checks to determine if corrections to similar events are correcting the issues. b) Deviation UE 201022310, opened on 19 September 2023, was for a failed HEPA filter leak test			
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for the (b)(4) Filling Line - in (b)(4) Maintenance activity performed on (b)(4) was determined to cause damage to the filter (b)(4), but this was only found by chance due to a separate regularly scheduled (b)(4) HEPA filter calibration (b)(4) where the filter leak test failed. Between (b)(4) batches of product were filled in the (b)(4) with a defective HEPA filter. Product quality was reviewed and it was assured there was no product impact or environmental area impact, but the CAPA effectiveness was lacking. The CAPA included an awareness training to maintenance technicians, but there is no thorough CAPA to assess impacts of maintenance and to assure that aseptic operations are protected to prevent a similar incident in the future. c) The firm has not established CAPA effectiveness for Invalid QC tests, that have rates as high as (b)(4) for Bexsero (DS) - (b)(4) on (b)(4) and (b)(4) for Bexsero (DS) - (b)(4)			
OBSERVATION 3 Employees engaged in the manufacture and processing of a drug product lack the training required to perform their assigned functions. Specifically, a) Critical cGMP training and operator qualifications are sometimes lapsed to be expired. The training qualifications are not always managed effectively to prevent gaps or lapses in training for operators who perform critical functions including aseptic operations and visual inspections and to ensure retraining is planned in a timely manner. Expired operator qualifications were			
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found for critical aseptic production activities in (b)(4) and manual visual inspections of sterile product. The firm does have methods to prevent operators with expired training from performing the specific tasks, but the communication to operators was reported to be (b)(4) and lacked a systematic approach to ensuring adequate training is complete.															
<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left; padding: 5px;">Activities</th> <th style="text-align: left; padding: 5px;">Percentage of Operators Expired Qualification</th> </tr> </thead> <tbody> <tr> <td style="padding: 5px;">Aseptic (b)(4)</td> <td style="padding: 5px;">(b)(4)</td> </tr> <tr> <td style="padding: 5px;">(b)(4)</td> <td style="padding: 5px;">(b)(4)</td> </tr> <tr> <td style="padding: 5px;">Grade - Intervention</td> <td style="padding: 5px;">(b)(4)</td> </tr> <tr> <td style="padding: 5px;">Line (b)(4)</td> <td style="padding: 5px;">(b)(4)</td> </tr> <tr> <td style="padding: 5px;">Manual Visual Inspection</td> <td style="padding: 5px;">(b)(4)</td> </tr> </tbody> </table>				Activities	Percentage of Operators Expired Qualification	Aseptic (b)(4)	(b)(4)	(b)(4)	(b)(4)	Grade - Intervention	(b)(4)	Line (b)(4)	(b)(4)	Manual Visual Inspection	(b)(4)
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b) At least 5 deviations in 2023, 2 in 2022, and 2 in 2021 were for operators with expired critical training qualifications while performing production activities including manual visual inspections, Grade - interventions, and other aseptic work. Deviations for 2023 included UE 200972673, 200980191, 200992933, 201002799, and 201012203. Specific CAPAs included (b)(4) training, but the firm did not establish a master deviation or master CAPA for related events and did not establish a CAPA effectiveness check to ensure that this repeated issue does not continue. Deviations were not extended to multiple products and batches potentially impacted.															
c) The firm's site training coordinator, the Quality Unit, training coordinators for each															
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(b)(4) and other relevant managers do not cross correlate the general cGMP and critical training qualification rates with training-related deviations to ensure that training needs are met to prevent future deviations.														
OBSERVATION 4 Not all adverse drug experiences that are both serious and unexpected have been reported to FDA within 15 calendar days of initial receipt of the information. Specifically, a. The firm's pharmacovigilance reporting of adverse drug events in year 2023 listed the following number of events were reported to the agency later than the required time. <table border="1" style="width: 100%; border-collapse: collapse; margin-top: 10px;"> <thead> <tr> <th style="width: 33%;">Vaccine</th> <th style="width: 33%;">Number of events reported late to agency in 2023</th> <th style="width: 33%;">Number of Days Late</th> </tr> </thead> <tbody> <tr> <td>Shingrix</td> <td>337</td> <td>1 to 122</td> </tr> </tbody> </table> The firm reported that some of the events for Shingrix were due to a common social media information event, but this was not defined. No explanation was given to why other adverse events were reported late or to the extent of number of days. b. The following additional vaccine adverse events were reported to the agency later than the 30-day requirement. <table border="1" style="width: 100%; border-collapse: collapse; margin-top: 10px;"> <thead> <tr> <th style="width: 33%;">Vaccine</th> <th style="width: 33%;">Number of events reported late to agency in 2023</th> <th style="width: 33%;">Number of Days Late</th> </tr> </thead> <tbody> <tr> <td style="height: 30px;"></td> <td></td> <td></td> </tr> </tbody> </table>			Vaccine	Number of events reported late to agency in 2023	Number of Days Late	Shingrix	337	1 to 122	Vaccine	Number of events reported late to agency in 2023	Number of Days Late			
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<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 35%;">Menveo</td> <td style="width: 30%;">1</td> <td style="width: 35%;">124</td> </tr> <tr> <td>Bexsero</td> <td>1</td> <td>74</td> </tr> <tr> <td colspan="3" style="text-align: center;">(b)(4)</td> </tr> </table>				Menveo	1	124	Bexsero	1	74	(b)(4)		
Menveo	1	124										
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(b)(4)												
OBSERVATION 5 Established laboratory control mechanisms are not followed. Specifically, the following was observed: - While observing QC release testing pertaining to the Menveo Full Liquid (DP) Quantitative determination of (b)(4) on (b)(4) assay for batches (b)(4) (b)(4) on 01/18/2024, it was observed that testing analyst (b)(4) did not lock (b)(4) laptop workstation utilized to record the assay within (b)(4) on multiple occasions when leaving (b)(4) workbench while conducting the assay. This activity does not follow firm procedure QC LSOP 9000054316 v10 "Good practices for computerized lab system" part 4.2 stating (b)(4) - While observing QC release testing pertaining to Bexsero (DS) Quantitative Determinations of (b)(4) in (b)(4) assay on 01/19/2024, it was observed that testing analyst (b)(4) did not lock (b)(4) laptop workstation utilized to record the assay within (b)(4) when leaving (b)(4) workbench while conducting the assay. This activity does not follow firm procedure QC LSOP 9000054316 v10 "Good practices for computerized lab system" part 4.2 stating (b)(4)												
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NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

Andrea D'Amato, Site Director

FIRM NAME	STREET ADDRESS
GlaxoSmithKline Vaccines Srl	Localita Bellaria

CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
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1/08/2024(Mon), 1/09/2024(Tue), 1/10/2024(Wed), 1/11/2024(Thu), 1/12/2024(Fri), 1/16/2024(Tue),
1/17/2024(Wed), 1/18/2024(Thu), 1/19/2024(Fri), 1/22/2024(Mon), 1/23/2024(Tue), 1/24/2024(Wed),
1/25/2024(Thu), 1/26/2024(Fri)

Roger F Zabinski
Investigator - Team Biologics
Signed By: Roger F. Zabinski -S
Date Signed: 01-26-2024 04:09:54

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	Travis S Bradley, Investigator Roger F Zabinski, Investigator - Team Biologics	1/26/2024

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."