

CBER DMPQ CMC/Facility BLA Review Memorandum

BLA STN 125819/0

**Established Name: Meningococcal Groups A, B, C, W and Y Vaccine
Proprietary Name: PENMENVY**

Reviewer's Name: Jared Greenleaf, Consumer Safety Officer, OCBQ/DMPQ/MRB1

1. **BLA#:** STN 125819/0
2. **APPLICANT:** GlaxoSmithKline Biologicals S.A., US License Number 1617
3. **PRODUCT NAME/PRODUCT TYPE**

Meningococcal Groups A, B, C, W and Y Vaccine; PENMENVY

4. **GENERAL DESCRIPTION OF THE FINAL PRODUCT**

a. **Pharmacological category**

Vaccine

b. **Dosage form**

Suspension for injection

c. **Strength/Potency**

0.5 mL single dose after reconstitution

d. **Route of administration**

Intramuscular (IM)

e. **Indication(s)**

For active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroups A, B, C, W, and Y in individuals 10 through 25 years of age.

5. **MAJOR MILESTONES**

Application Receipt Date	February 15, 2024
Filing Date	April 15, 2024
Midcycle Date	August 16, 2024
Late-cycle Date	October 30, 2024
Final Action Due Date	February 14, 2025

6. **DMPQ CMC/FACILITY REVIEW TEAM**

Reviewer/Affiliation	Section/Subject Matter
Jared Greenleaf, CSO, OCBQ/DMPQ/MRB1	<ul style="list-style-type: none"> 3.2.S MenACWY polysaccharides and conjugates (b) (4) 3.2.P MenACWY Formulation (b) (4) 3.2.P MenACWY Fill/Lyo (b) (4) 3.2.P MenACWY Visual Inspection (b) (4) 3.2.S OMV) (b) (4) (b) (4)) 3.2.S Recombinant proteins (b) (4) 3.2.P MenB DP (b) (4) 3.2.A.1 Facilities and Equipment (b) (4)

S) REVIEWED

Date Received	Submission	Comments/ Status
February 15, 2024	STN 125819/0	Original Submission
May 3, 2024	Amendment STN 125819/0.4	Commitment to provide quality system information
May 22, 2024	Amendment STN 125819/0.7	Provided quality system information
June 17, 2024	Amendment STN 125819/0.10	Clarification about facility and equipment information
July 31, 2024	Amendment STN 125819/0.18	Wavre equipment and process information (b) (4)
October 10, 2024	Amendment STN 125819/0.32	decontamination information
December 9, 2024	Amendment 125819/0.51	Updated MenACWY Lyo shelf life information
December 12, 2024	Amendment STN 125819/0.53	Updated MenABCWY Reconstituted

Date Received	Submission	Comments/ Status
		Vaccine shelf life information

8. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

The Center for Biologics Evaluation and Research (CBER) received a Biologics License Application (BLA) for Penmenvy under STN 125819/0 from GlaxoSmithKline Biologicals S.A. (referred to as GSK, the applicant, or the firm) on February 15, 2024. Penmenvy drug product (DP), also referred to as MenABCWY Vaccine, is a sterile combination product consisting of the MenACWY Lyo component, filled in a single dose 3 mL glass vial, and a MenB Liquid component, filled in a 1.25 mL glass syringe. A single dose consists of 0.50 mL of the MenABCWY Vaccine following reconstitution of the MenACWY Lyo component with the full contents of the MenB Liquid component.

The MenACWY Lyo component is made from CRM₁₉₇ (Cross-Reactive Material) conjugated polysaccharide antigens derived from *Neisseria meningitidis*, serogroups A, C, W, and Y. The conjugated polysaccharide antigens are manufactured using the same facilities, equipment, processes, and critical utilities as the currently licensed vaccine Menveo (BL 125300).

The MenB Liquid component consists of three recombinant proteins derived from *N. meningitidis* serogroup B, strains NZ98/254, MC58, and 2996, and Outer Membrane Vesicle (OMV) derived from *N. meningitidis* serogroup B, strain NZ98/254. The MenB Liquid component, recombinant protein antigens, and OMV are manufactured using the same facilities, equipment, processes, and critical utilities as the currently licensed vaccine Bexsero (BL 125546). The only difference between the MenB Liquid component and Bexsero is the (b) (4) for the MenB Liquid component is (b) (4) is provided for reconstitution of the MenACWY Lyo component.

Penmenvy is administered as an intramuscular suspension for injection for active immunization to prevent invasive disease caused by *N. meningitidis* serogroups ABCWY.

DMPQ waived inspections of the following facilities on August 16, 2024:

- GlaxoSmithKline Biologicals S.A., Avenue Fleming 20, 1300 Wavre, Belgium (FEI#: 3003973577) for (b) (4)
 - The following licensed products are manufactured (b) (4)

- Cross-contamination on the (b) (4) is low risk due to procedures for clearance, product changeover, and equipment and facility cleaning and disinfection.
- GSK Vaccines S.r.l., Locality Bellaria-Rosia, 53018 Sovicille, Italy (FEI#: 3006738517) for manufacture of MenACWY polysaccharides, CRM₁₉₇, conjugated MenACWY polysaccharides, OMV, and the MenB Liquid component. The facility is also responsible for inspection, packaging, labeling, testing (QC and stability), and storage of DS and DP.
 - Licensed products manufactured on (b) (4) are Bexsero and (b) (4)

B. RECOMMENDATION
I. APPROVAL

Based on the information submitted to BLA STN 125819/0, and in conjunction with the inspectional compliance history evaluations, the production processes, facilities, equipment, and controls appear acceptable for the licensure of PENMENVY, and approval is recommended.

II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Jared Greenleaf, CSO, OCBQ/DMPQ/MRB1	Concur	
Kathleen Jones, Branch Chief, OCBQ/DMPQ/MRB1	Concur	
For, Carolyn Renshaw, Director, OCBQ/DMPQ	Concur	

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Introduction

This memo is organized based on eCTD format according to information provided by GSK under BLA STN 125819/0. As such, there are individual Module 3 sections (i.e., 3.2.S Drug Substance) for each meningococcal polysaccharide (PS) antigen, conjugated polysaccharide antigen, and the CRM₁₉₇ carrier protein used for conjugation. Following these Module 3 section is the 3.2.P Drug Product section for MenACWY Lyo.

After the MenACWY DS and DP sections, the reader will find 3.2.S DS sections for the MenB recombinant proteins and OMV. Following these sections are 3.2.P Drug Product sections for MenB Liquid and MenABCWY finished product.

In the submission, there is one section for 3.2.A.1 Facilities and Equipment. However, since the review covers four facilities, the facility and equipment information in this memo is organized into separate 3.2.A.1 Facilities and Equipment sections for each facility (i.e., Rosia, (b) (4) [REDACTED]).

Module 3

3.2.S DRUG SUBSTANCE [MenA Polysaccharide][Rosia]

(b) (4) [REDACTED]

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

Reviewer's comment: See section 3.2.A Appendices for a complete list of DS manufacturers.

3.2.S.2.2 Description of Manufacturing Process

29 pages determined to be not releasable: (b)(4)

are the same as for material used for the Menveo vaccine. Evaluation of the analytical stability tests is deferred to OVR.

3.2.P DRUG PRODUCT [MenACWY Lyo](b) (4)

3.2.P.1 Description and Composition of the Drug Product

The MenACWY Lyo component is a lyophilized powder containing four *Neisseria meningitidis* oligosaccharides (MenA, MenC, MenW, MenY), which are each conjugated to a CRM₁₉₇ protein. The MenACWY Lyo component is reconstituted with the MenB Liquid component to obtain the final combined MenABCWY reconstituted vaccine. The composition of the MenACWY Lyo component, including active substances and excipients, was provided in Section 3.2.P.1 Description and Composition of the Drug Product, Table 1.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

Reviewer's comment: See section 3.2.A Appendices for a complete list of DP manufacturers.

3.2.P.3.3 Description of Manufacturing Process

The MenACWY Lyo process consists of formulation, aseptic filling, lyophilization, and storage. The formulation process consists of preparing a homogeneous solution of (b) (4)

The MenACWY Lyo (b) (4)

. The vials are then visually inspected and sampled for release testing. Inspected and approved vials are placed in boxes, palletized, and stored at the warehouse (at 2 – 8°C), awaiting labelling and packaging.

3.2.P.3.4 Controls of Critical Steps and Intermediates

The MenACWY Lyo (b) (4)

The MenACWY Lyo (b) (4) is sampled before (b) (4) . CCIT (b) (4) of the final container is performed after capping. The firm provided results for these tests for the MenACWY Lyo PPQ (b) (4) and post PPQ lots (b) (4) in Section 3.2.P.3.4 Control of Critical Steps In-process Quality Decisions tests – Batch Analysis Data. All results met the acceptance criteria.

Reviewer's comment: *The in-process PPQ batch analyses results provide support for consistent MenACWY Lyo manufacturing at (b) (4) from a microbial control perspective.*

The current Critical Process Parameters (CPPs) were provided in Table 2 of Section 3.2.P.3.3 Description of Manufacturing Process and Process Controls – Formulation and Table 1 of Section 3.2.P.3.3 Description of Manufacturing Process and Process Controls – Filling and Lyophilisation. These Tables are summarized in the Table below.

(b) (4)

(b) (4)

Reviewer's comment: The (b) (4) testing appears acceptable. In Figure 2 of Section 3.2.P.3.3 Description of Manufacturing Process and Process Controls – (b) (4), the firm provided an example lyophilization chart with parameters that corresponds to the parameters listed above, including (b) (4). The chart also shows the (b) (4), which is not a CPP.





Container Closure Integrity Test Validation

(b) (4)

1. **Identify the main components of the system.**
 2. **Define the scope and objectives of the project.**
 3. **Develop a detailed project plan.**
 4. **Implement the plan and monitor progress.**
 5. **Evaluate the results and provide feedback.**

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(b) (4)



3.2.P.5 Control of Drug Product

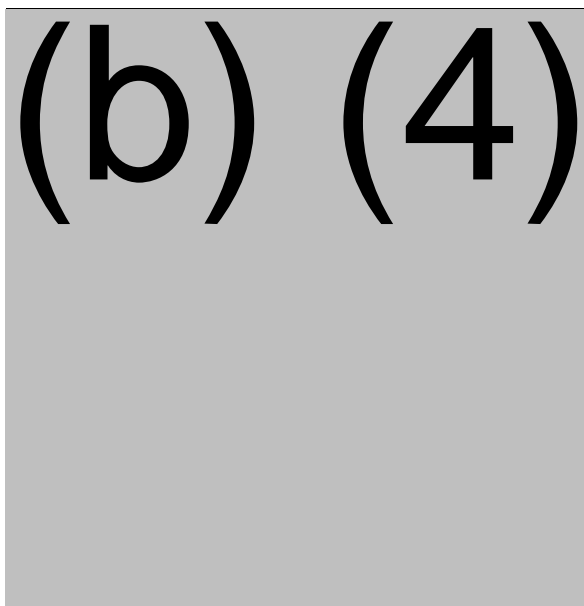
3.2.P.5.1 Specification(s) and 3.2.P.5.6 Justification of Specification(s)

The specification includes tests for sterility (no growth) using (b) (4), bacterial endotoxin (b) (4) using the (b) (4) method (i.e., (b) (4)), and visual inspection (free from visible particles).

Reviewer's comment: *The sterility and bacterial endotoxin tests are in accordance with (b) (4) requirements (sterility: (b) (4) endotoxin: (b) (4)). Evaluation of specifications not germane to microbial control is deferred to OVR.*

3.2.P.5.4 Batch Analyses

GSK provided MenACWY Lyo batch information for batches that were originally manufactured at (b) (4) and (b) (4) for Clinical Phases 1, 2, and 3, and commercial scale PPQ and post-PPQ lots. The batches are used in this submission to support MenACWY development, Clinical (Phases 1-3), MenACWY Lyo PPQ, MenACWY Lyo post-PPQ. MenACWY Lyo PPQ and post-PPQ batch genealogy is provided below.



All MenACWY Lyo batches met the acceptance criteria for sterility (no growth), endotoxin (b) (4) /vial), and visible particles (no visible particles).

Reviewer's comment: *The microbial results appear acceptable. The manufacturing process appears capable of producing consistent results in terms of sterility assurance and microbial control. Evaluation of tests not germane to microbial control is deferred to OVR. Evaluation of clinical batches is deferred to OVR.*

3.2.P.7 Container Closure System

The MenACWY Lyo component is packaged in 3 ml vial containers, closed with 13 mm bulk lyo stoppers, and secured with flip-off caps.

The 3 mL vial is Type (b) (4) uncolored glass supplied by (b) (4). The vial meets (b) (4) Glass containers for pharmaceutical use" and (b) (4) requirements per (b) (4) Glass containers". The vials are (b) (4) with an (b) (4). The vials are sterilized (b) (4) before use. A description of the vial and the in-house tests was provided in Section 3.2.P.7 Container Closure System – Vial Container, Table 2.

The 13 mm lyo stopper is made from bromobutyl Type (b) (4) rubber and supplied by (b) (4). The stopper meets (b) (4) Rubber closures for containers for freeze-dried powders” and (b) (4) Elastomeric closures for injection”. The stoppers are (b) (4) sterilized internally at GSK. A description of the stopper and the in-house tests was provided in Section 3.2.P.7 Container Closure System – Vial stoppers, Table 2.

The flip-off cap is made from colored polypropylene top fixed on an aluminum varnished cap and supplied by (b) (4). The flip-off cap is not in contact with the product and are not sterilized. A description of the flip-off cap and the in-house tests was provided in Section 3.2.P.7 Container Closure System – Vial stoppers, Table 2.

Reviewer’s comment: In amendment 125819/0/18 (received July 31, 2024), the firm confirmed that the CCS components of the MenACWY Lyo component are the same as the previously approved (b) (4) vaccines. Additionally, the CCS components are processed and tested internally at GSK in the same manner as used for the previously approved (b) (4) vaccines, regardless of the component supplier.

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data

The PPQ lots were placed on stability (long-term (2 – 8°C for 48 months), accelerated (b) (4)). Currently the long-term study is ongoing and there are 24 months of data available. Phase 3 clinical stability (manufactured at (b) (4)) data provided to support a 36-month shelf life. The accelerated (b) (4) conditions included CCI testing stability samples at release and expiry. The long-term condition included CCIT and sterility (0, 12, 24, and 36 months).





Reviewer’s comment: The stability data within DMPQ purview appear to support the storage of MenACWY Lyo final container for up to (b) (4) months at 2 – 8°C. All tests for sterility and CCIT met the acceptance criteria for the PPQ, post-PPQ, and Phase Clinical lots. Evaluation of tests not germane to microbial control is deferred to OVR. In amendment 125819/0.51, GSK updated the proposed shelf life for MenACWY Lyo from (b) (4)-months to 18-months.

3.2.S DRUG SUBSTANCE [MenB (b) (4)]

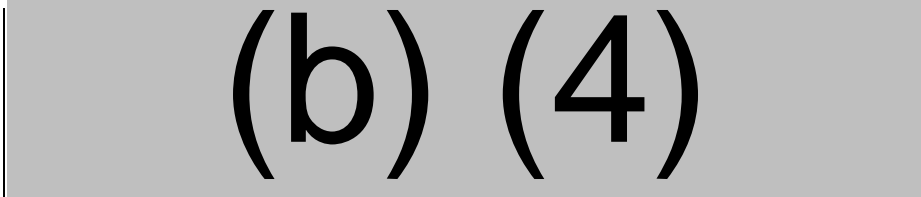
(b) (4)

10 pages determined to be not releasable: (b)(4)






(b) (4)



(b) (4)



(b) (4)



3.2.S.7 Stability

3.2.S.7.1 Stability Summary and Conclusion and 3.2.S.7.3 Stability Data

The 48-month shelf life is supported by stability data from Bexsero process validation and commercial batches. The recommended storage condition is 2 – 8°C.

Reviewer's comment: *The shelf life and storage conditions are the same as for material used for the Bexsero vaccine. Evaluation of the analytical stability tests is deferred to OVR.*

3.2.P DRUG PRODUCT [MenB/OMV NZ][Rosia]

3.2.P.1 Description and Composition of the Drug Product

The MenB Liquid component is a suspension for injection consisting of *N. meningitidis* serogroup B recombinant protein antigens (rp287-953, rp936-741, and rp961c) and Outer Membrane Vesicles (OMV) purified from *N. meningitidis* serogroup B. The constituent antigens are adsorbed to aluminum hydroxide. The MenB Liquid component, in a pre-filled syringe, is used to reconstitute the MenACWY Lyo component to obtain the final combined MenABCWY reconstituted vaccine (RV). The composition of the MenB Liquid component, including active substances and excipients, was provided in Section 3.2.P.1 Description and Composition of the Drug Product, Table 1.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

Reviewer's comment: *See section 3.2.A Appendices for a complete list of DP manufacturers.*

3.2.P.3.3 Description of Manufacturing Process

The MenB Liquid manufacturing process consists of (b) (4)

[Redacted text block]

(b) (4)

[Redacted text block]

1 page determined to be not releasable: (b)(4)

Reviewer's comment: The extractable volume results from the Filling Process 2.2 PPQ consistently met the needed volume for MenACWY reconstitution (0.5 mL) and appears to consistently yield a (b) (4) than the (b) (4) PPQ.

This indicates that the filling equipment is capable of filling product vials consistently within limits necessary for reconstitution. As reported by the firm, the processes are otherwise the same. The information provided appears acceptable. Evaluation of the results for extractable volume is deferred to the product office reviewer.

3.2.P.5 Control of Drug Product

The specification includes tests for sterility (no growth) using (b) (4), bacterial endotoxin (b) (4)

, and visual inspection (free from visible particles). Additionally, the (b) (4) is also tested for sterility.

Reviewer's comment: The sterility and bacterial endotoxin tests are in accordance with (b) (4) requirements (sterility: (b) (4) endotoxin: (b) (4) and are consistent with the previously approved Bexsero vaccine. Evaluation of specifications not germane to microbial control is deferred to OVR.

3.2.P.7 Container Closure System

The MenB Liquid component container closure system (CCS) consists of a 1.25 mL syringe barrel with Luer Lock closure, a (b) (4) rubber tip cap, a syringe plunger stopper, and a syringe plunger rod. The syringe barrel, rubber tip cap, and plunger stopper are (b) (4). The syringe barrel and rubber tip cap are sterilized (b) (4). The plunger stopper is sterilized (b) (4). The CCS components meet (b) (4) requirements for glass containers and elastomeric enclosures. Syringe components are supplied by (b) (4).

. A description of the CCS components and the in-house tests was provided in Section 3.2.P.7 Container Closure System.

Reviewer's comment: The CCS components reported for the MenB Liquid component are the same as the current CCS used for the Bexsero vaccine.

3.2.P.8 Stability

PPQ lot (b) (4) was placed on long-term stability at (b) (4) months. Currently the long-term study is ongoing and there are 24 months of data available. Additionally, post-PPQ lot (b) (4) was placed on long-term stability at (b) (4) months, with data through 18 months available. PPQ lot (b) (4) was tested for endotoxin (b) (4).

(b) (4); 0, 3, 6, 9, 12, 18, and 24-months), sterility (no growth; 0, 6, 12, and 24-months), and CCIT ((b) (4); 0, 12, and 24-months). Post-PPQ lot (b) (4) was tested for endotoxin (b) (4); 0, 3, 6, 9, 12, 18, and 24-months), sterility (no growth; 0, and 12-months), and CCIT (b) (4); 0, and 12-months). All acceptance criteria were met.

MenB Liquid Phase 3 clinical lot DBX017A, manufactured in 2019, was placed on long-term stability for 48 months at 2 – 8°C in order to support the shelf life of the MenB Liquid component. Stability tests included endotoxin (b) (4); 0, 6, 12, 18, 24, 30, 36, 42, and 48-months), sterility (no growth; 0, 12, 24, 36, and 48-months), and CCIT (b) (4); 6, 12, 24, 36, and 48-months). All acceptance criteria were met.

The firm provided additional Bexsero stability data (PPQ and commercial material) to support a 48-month shelf life for lots manufactured using the current Bexsero process and syringe.

Reviewer's comment: *The stability studies appear to support the storage of MenB Liquid PFS for up to 48 months at 2 – 8°C. All tests for sterility, endotoxin, and CCIT met the acceptance criteria for the PPQ, post-PPQ, and clinical lots. The supportive Bexsero lots were reviewed and approved under STN 125546/786 (approved July 15, 2021), STN 125546/882 (approved March 15, 2022), and STN 125546/963 (approved February 24, 2023). The information provided appears acceptable. Evaluation of specifications not germane to microbial control is deferred to OVR.*

3.2.P DRUG PRODUCT [MenABCWY][Rosia](b) (4)

3.2.P.1 Description and Composition of the Drug Product

The MenABCWY vaccine is composed of two components: 1) MenACWY Lyo component in a vial and 2) MenB Liquid component in a pre-filled syringe (PFS). The MenABCWY vaccine is indicated for active immunization to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, B, C, W and Y. The MenABCWY vaccine is reconstituted to produce the MenABCWY reconstituted vaccine (MenABCWY RV) by adding the entire contents of the MenB Liquid PFS to the MenACWY Lyo vial, thereby ensuring delivery of a nominal dose of 0.5 mL. The composition of the MenABCWY RV was provided in Section 3.2.P.1 Description and Composition of the Drug Product, Table 1.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

Reviewer's comment: *See section 3.2.A Appendices for a complete list of DP manufacturers.*

3.2.P.3.3 Description of Manufacturing Process and Process Controls

The MenACWY Lyo vials and MenB Liquid PFS are labeled via automatic labeling machines. A plunger rod is threaded into the stopper of each syringe and the syringes are labeled with a self-adhesive label. The vial and syringe labels are overprinted with lot number and expiration date. The firm states that additional variable data is included on the label if applicable. The vials and syringes are then placed in combo cartons and the cartons are labeled with the lot number and expiration date. The expiration date of the carton is the earliest date between the MenACWY Lyo component and the MenB Liquid component. The carton batch number is a 5-digit alphanumeric code generated by the firm's inventory management system (i.e., SAP). The MenACWY Lyo final container (FC) batch number and MenB Liquid FC batch number are replaced with the new 5-digit batch number and A for the MenACWY Lyo component and B for the MenB Liquid component. The firm provided the following example: Combo Carton (XYZ12), MenACWY Lyo (XYZ12/A), and MenB Liquid (XYZ12/B). The cartons are placed in shipping boxes, the shipping boxes are identified, palletized, and stored at 2 – 8°C.

Finished Product Shipping and Validation

Shipping validation information was provided in Section 3.2.A.1 Facilities and Equipment – MenABCWY vaccine – Cold Chain Transport and Validations. The MenABCWY finished product shipping information is covered under Section 3.2.P.3.3 of this memo since it involves multiple facilities. MenACWY Lyo FC are shipped to (b) (4) building (b) (4), where it is incorporated into the finished product. The MenB Liquid FC is transferred from (b) (4) or shipped to (b) (4) to be incorporated into the finished product. From Rosia or (b) (4), the finished product is shipped to distribution sites in the U.S. The MenACWY Lyo FC and MenB FC are transferred (b) (4)

Reviewer's comment: *The shipping methods described below (i.e., road, sea, and air) for the finished product are the same that are used for final container product. Additionally, the final containers are (b) (4)*

The same external packaging is used for finished product. Final container product is also maintained at 2 – 8°C. As such, the shipping validation information provided below is applicable to final container product filled in glass vials and syringes.

(b) (4)

1 page determined to be not releasable: (b)(4)

(b) (4)

Reviewer's comment: The shipping methods proposed for MenABCWY finished product are currently used by GSK to ship currently licensed vaccine products from the same facilities used manufacture MenABCWY. The shipping information has been provided previously under BLA STN 125775/0 with the exception of (b) (4) qualification report TTC-0000019514. The (b) (4) is a newer version of the (b) (4), and based on the data provided, outperforms the (b) (4) in terms of temperature duration at 2 – 8°C. The temperature studies provided for the shipping methods (road, air, sea) were performed with (b) (4) to represent worst-case in terms of (b) (4). The information provided appears acceptable.

3.2.P.5 Control of Drug Product

3.2.P.5.1 Specification(s) and 3.2.P.5.6 Justification of Specification(s)

The specification for the MenABCWY Reconstituted Vaccine (RV) includes tests for appearance (opalescent liquid (white suspension)), visible particles (free from visible particles), and endotoxins (b) (4).

Appearance is controlled in order to verify the visual compliance with the description reported in the acceptance criterion. The test is required by (b) (4).

Endotoxin level of MenABCWY RV is measured by (b) (4) test. The test is performed according to (b) (4). The endotoxin specification is the same as the MenB Liquid specification and Bexsero vaccine specification.

Reviewer's comment: The tests are performed according to (b) (4) methods and are consistent with the previously approved Bexsero vaccine.

3.2.P.8 Stability

Stability studies were performed to confirm the quality of MenABCWY RV after storage of component lots (i.e., MenACWY Lyo and MenB Liquid) at different timepoints. The studies consisted of subjecting PPQ and post-PPQ lots to long-term (2 – 8°C for (b) (4) months), accelerated (b) (4) months, (b) (4) conditions.

The long-term tests include visual appearance (time-0, 3, 6, 9, 12, 18, 24, and 30), visible particles (time-0, 3, 9, 12, 24, and 30), endotoxins (time-0, 12, 24, and 30), and pyrogenicity (time-0, 12, 24, and 30). The acceptance criteria were the same as listed above in Section 3.2.P.5.1 Specifications. Data through the 30-month timepoint were provided for lots PPQ lots (b) (4)

. Data through the 18-month timepoint were provided for lots post-PPQ lot (b) (4). All acceptance criteria were met.

The accelerated (b) (4) condition included tests for visual appearance and visible particles. The tests were performed at all timepoints, that is 0, 1, 3, 6-months and 0, 1, 2, 3-weeks, respectively. The study consisted of lots (b) (4). All acceptance criteria were met.

An in-use study was also performed and consisted of storing the reconstituted vaccine for (b) (4) at the beginning of shelf life of the MenACWY Lyo and MenB Liquid components and at the (b) (4) timepoints. MenABCWY RV lots (b) (4) were used for the study. The samples were subjected to analytical tests and visual inspection for appearance. All samples met the acceptance criterion for visual inspection. Based on the data provided, the firm proposes an in-use shelf life of (b) (4) after reconstitution when stored at (b) (4).

Reviewer's comment: The firm states that in-use stability is supported up to (b) (4) after reconstitution. The visual appearance results appear acceptable. Evaluation of the analytical data is deferred to OVR. The long-term stability data appears to support the MenACWY Lyo and MenB Liquid shelf lives. In amendment 125819/0.53, GSK updated the proposed shelf life of MenABCWY reconstituted vaccine (RV) from (b) (4) after reconstitution to immediate administration after reconstitution.

3.2.A APPENDICES

GSK provided an overview of the MenABCWY vaccine facilities in Section 3.2.A.1 Facilities and Equipment – MenABCWY vaccine – Facilities Overview. The facilities used to manufacture the MenACWY Lyo component, the MenB liquid component, and the co-packaged MenABCWY vaccine are provided in the table below.

Facility Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?	RMS-BLA entry required?	Comments
<p>Facility: GSK Vaccines S.r.l., Locality Bellaria Rosia, 53018 Sovicille, Italy FEI#: 3006738517 DUNS#: 445558679</p> <ul style="list-style-type: none"> MenA, C, W, and Y polysaccharides, carrier protein (CRM₁₉₇), and conjugated MenA-, C-, W-, and Y-CRM DS manufacture. OMV manufacture for MenB Liquid component. QC testing and batch release of the 3 recombinant protein DSs. MenB Liquid component formulation and filling. Inspection, packaging, labeling, QC and stability testing, and storage of DS and DP. Manufacture, storage, and QC testing of (b) (4) for the 3 recombinant proteins and OMV. 	Waiver	Yes	Yes	<p>ORA Surveillance Inspection January 2024 VAI (Covered Bexsero & Menveo products)</p>
<p>Facility: (b) (4)</p> <p>(b) (4)</p> <ul style="list-style-type: none"> (b) (4) of recombinant proteins. QC testing and warehousing 	Waiver	Yes	Yes	<p>CDER Surveillance Inspection (b) (4) VAI (b) (4)</p>
<p>Facility: GlaxoSmithKline Biologicals S.A., Avenue Fleming 20, 1300 Wavre, Belgium FEI#: 3003973577 DUNS#: 376996273</p>	Waiver	Yes	Yes	<p>ORA Surveillance Inspection (b) (4) NAI</p>

Facility Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?	RMS-BLA entry required?	Comments
<ul style="list-style-type: none"> • (b) (4) 				(Multiple vaccines)
Facility: GSK Vaccines GmbH, (b) (4) <ul style="list-style-type: none"> • Manufacture of aluminum hydroxide excipient; warehousing 	Not required	No	Yes	N/A
Facility: (b) (4) <ul style="list-style-type: none"> • Warehousing operations 	Not required	No	Yes	The facility is operated by GSK and rented from (b) (4)
Facility: (b) (4) GlaxoSmithKline Vaccines, (b) (4) <ul style="list-style-type: none"> • Packaging and labeling, QC testing (identity testing), warehousing, and release of MenABCWY final product 	Waiver	Yes	Yes	CBER PLI for (b) (4) VAI
Facility: GlaxoSmithKline Vaccines S.r.l., Via Fiorentina 1, 53100 Siena, Italy FEI#: 3007780504 DUNS#: 442017901	Not required	No	Yes	N/A

Facility Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?	RMS-BLA entry required?	Comments
• (b) (4)				
Facility: (b) (4)				
• Warehousing operations	Not required	No	Yes	N/A

DS: drug substance, DP: drug product, (b) (4), QA: quality assurance, QC: quality control; DBA: doing business as

Reviewer's comment: The concurred inspection waiver (IW) for the sites listed as "waiver" in the table above is uploaded to CBER Connect.

3.2.A.1 Facilities and Equipment [Rosia]

MenABCWY vaccine components are manufactured in buildings (b) (4), and (b) (4) at the GSK facility in Rosia, Italy. Rosia is a multi-product facility used to manufacture the following:

- MenA, MenC, MenW, and MenY polysaccharide intermediates for use in the manufacture of the MenACWY Lyo component (b) (4),
- Carrier protein CRM₁₉₇ used to conjugate the polysaccharides (b) (4),
- MenA-CRM, C-CRM, W-CRM, and Y-CRM conjugated intermediates for use in the manufacture of the MenACWY Lyo component (b) (4),
- Outer Membrane Vesicles (OMV) for use in the manufacture of the MenB Liquid component (b) (4)
- MenB Liquid component for the MenABCWY vaccine (b) (4),
- MenABCWY vaccine packaging and labeling (b) (4).

Building (b) (4)

In Section 3.2.A.1 Facilities and Equipment – Building (b) (4) – Chapter 1 – Facility Description, GSK provided a list of shared and dedicated areas, flow charts of manufacturing unit operations, and links to facility drawings.

(b) (4) is a (b) (4) building that includes a (b) (4) (Level (b) (4)), a (b) (4) floor (Level (b) (4)) and (b) (4) floors above the (b) (4) floor (Levels (b) (4)). Levels (b) (4) are manufacturing areas, which are supported by technical areas located on Levels (b) (4). Level (b) (4) is dedicated to manufacture the meningococcal polysaccharide

intermediates (b) (4) Suite (b) (4), CRM₁₉₇ (b) (4) Suite (b) (4), and the conjugated polysaccharide intermediates (b) (4) Suite (b) (4). The firm lists the Level (b) (4) rooms as shared because they are used to produce multiple meningococcal polysaccharide antigens. Level (b) (4) is dedicated to OMV manufacture in Suite (b) (4) and Suite (b) (4).

Reviewer's comment: In amendment 125819/0.10, GSK confirmed that the MenA, C, W, and Y manufacture, CRM manufacture, and conjugate manufacture is performed on the (b) (4) floor using the same manufacturing areas, product contact equipment, critical support equipment and critical utilities as those registered for Menveo (BL 125300). Additionally, OMV is manufactured on (b) (4) using the same manufacturing areas, product contact equipment, critical support equipment and critical utilities as those registered for Bexsero (BL 125546).

(b) (4) Equipment

In Section 3.2.A.1 Facilities and Equipment – Building (b) (4) – Chapter 2 – Equipment, Table 1-3, the firm listed dedicated, shared, and single use equipment used in (b) (4).

For CRM₁₉₇ manufacture, (b) (4)

(b) (4)

For polysaccharide and conjugate manufacture, (b) (4)

(b) (4)

For OMV manufacture, dedicated (b) (4)

(b) (4)

(b) (4) support equipment include (b) (4)





(b) (4)

Reviewer's comment: In amendment 125819/0.10, GSK confirmed that the MenA, C, W, and Y manufacture, CRM manufacture, and conjugate manufacture is performed on the (b) (4) floor using the same manufacturing areas, product contact equipment, critical support equipment and critical utilities as those registered for Menveo (BL 125300). Additionally, OMV is manufactured on the (b) (4) Level (b) (4) using the same manufacturing areas, product contact equipment, critical support equipment, and critical utilities as those registered for Bexsero (BL 125546). Therefore, since the equipment is already used to manufacture a licensed vaccine, the qualification did not require re-review to support this vaccine.



(b) (4) HVAC Systems

In Section 3.2.A.1 Facilities and Equipment – Building (b) (4) – Chapter 3 – HVAC, the firm provided information regarding the HVAC systems at (b) (4). The facility utilizes (b) (4) air handling units (AHUs) that supply air to the manufacturing areas. (b) (4) manufacturing areas, corridors, and airlocks are classified Grade (b) (4) (Grade (b) (4) air quality), with Grade (b) (4) in select Grade (b) (4) areas (i.e., (b) (4) room). (b) (4) has no Grade (b) (4) areas. Additional AHUs supply air to changing rooms and offices. Overall, HVAC system control, including air flow, pressure, temperature, humidity, monitoring, and alarms are managed via a building automation system (BAS).

(b) (4)



(b) (4)



Environmental Monitoring

The firm provided a list of past environmental monitoring validations (EMPQs) in Section 3.2.A.1 Facilities and Equipment – Building (b) (4) – Chapter 3 – HVAC, Table 27. Manufacturing and support areas are monitored for non-viable air particles, active air, passive air, and surfaces. The following acceptance criteria are used (based on the ISO (b) (4) Standard):

(b) (4)

The firm states that since 2019 EMPQs are performed only under (b) (4) conditions. Routine monitoring is conducted according to area classification. Grade (b) (4) are continuously monitored for non-viable particles, active air, and passive air during all critical steps. Surface monitoring is performed (b) (4) and at the end of each critical step. Grade (b) (4) areas are monitored for non-viables, and viables (b) (4) and Grade (b) (4) areas are monitored (b) (4).

Reviewer's comment: In amendment 125819/0.10, GSK confirmed that the MenA, C, W, and Y manufacture, CRM manufacture, and conjugate manufacture is performed on the (b) (4) floor using the same manufacturing areas, critical support equipment and critical utilities as those registered for Menveo (BL 125300). Additionally, OMV is manufactured on (b) (4) using the same manufacturing areas, critical support equipment, and critical utilities as those registered for Bexsero (BL 125546). The HVAC system qualifications and EMPQs were previously reviewed under the Menveo and Bexsero original applications and/or supplements and thus do not require re-review for this new product application.

(b) (4) Water Systems

Purified water (PW) and Water for Injection (WFI) are produced in Building (b) (4) from (b) (4) water supplied by Building (b) (4) and Building (b) (4) water from (b) (4) supplies (b) (4) systems (b) (4) to produce PW. (b) (4) water from (b) (4) supplies (b) (4) system (b) (4). The PW is distributed to (b) (4), clean steam (CS) generators and PW points-of-use (POUs). The (b) (4) supply WFI to (b) (4) which supply WFI POUs in the building. The CS generators supply the CS distribution systems, which in turn supply the CS POUs. A diagram of the (b) (4) water system was provided in Section 3.2.A.1 Facilities and Equipment – Building (b) (4) – Chapter 4 – Water Systems, Figure 1.

Routine monitoring of the WFI system for (b) (4) is conducted (b) (4), whereby the sampling sites are sampled at least (b) (4) on a rotating basis to cover all sample sites. Routine monitoring of the WFI system for (b) (4) is performed (b) (4). The following acceptance criteria are used:

(b) (4)

Reviewer's comment: The (b) (4) water systems were previously reviewed under the Menveo (BLA 125300/0) and Bexsero (BLA 125546/0) original applications and/or supplements. In amendment 125819/0.10, GSK confirmed that the existing systems used previously approved products are also used for the MenB Liquid component, OMV, and MenACWY component materials manufacture.

(b) (4) Process Gases

Process gas information was provided in Section 3.2.A.1 Facilities and Equipment – Building (b) (4) – Chapter 5 – Pure Steam, Compressed Air, Nitrogen Systems and Oxygen Systems. (b) (4) process gases consist of clean steam (CS), Compressed Air for Process (CAP), nitrogen, and oxygen. CS is used for (b) (4)

(b) (4) CAP (b) (4). Nitrogen is used

(b) (4). Oxygen (b) (4).

Routine monitoring of the CS system is performed (b) (4) by sampling throughout each (b) (4) to cover all sample points. The following acceptance criteria are used:

(b) (4)

Routine monitoring of the CAP system is performed (b) (4) by sampling throughout each (b) (4) to cover all sample points. The following acceptance criteria are used:

(b) (4)

Routine monitoring of the Nitrogen system is performed (b) (4) by sampling throughout each (b) (4) to cover all sample points. The following acceptance criteria are used:

(b) (4)

Reviewer's comment: The (b) (4) gas systems were previously reviewed under the Menveo (BLA 125300/0) and Bexsero (BLA 125546/0) original applications and/or supplements. In amendment 125819/0.10, GSK confirmed that the existing systems used previously approved products are also used for

the MenB Liquid component, OMV, and MenACWY component materials manufacture.

Contamination and Cross-Contamination Control

The firm provided contamination & cross contamination control information in Section 3.2.A.1 Facilities and Equipment – Building (b) (4) – Chapter 6 – Contamination & Cross Contamination Control. Control is achieved through facility design, equipment design, facility and equipment labeling, containment procedures, including air locks, closed systems, HVAC (pressure differentials and separate AHUs), facility flows, cleaning, disinfection, and decontamination procedures, gowning, and line clearance and product changeover procedures.

The facility is designed to provide durable, smooth, and easily cleanable surfaces. The critical operations are performed with sterilized equipment, assemblies, and disposable materials in appropriately classified areas. The glass windows are designed with rounded corners and wall perimeter coving profile. The ceiling is constructed of plastic laminate panels, and lights are sealed and flush with the ceiling. The building design is based on the principle of physical and operational segregation to prevent cross-contamination from other facilities and between production campaigns.

The building is designed with the following features: 1) Separate access for personnel and raw materials, 2) separate exits for product material, 3) use of magnetic key cards to restrict access to only authorized personnel, 4) dedicated utilities, 5) dedicated HVAC systems, 6) validated cleaning methods for multi-product and product contact equipment, and 7) dedicated manufacturing support areas such as washing rooms, storage rooms, and cold rooms.

Process equipment systems are designed with no dead legs and are self-draining to ensure that cleaning and sterilization or sanitization can be performed. Product contact surfaces are designed with materials and finishes that ensure cleanability. Systems are equipped with sterilizing grade liquid filters and vent filters, as necessary.

Personnel are trained to perform their assigned job functions according to GMP requirements. Personnel are trained and qualified regarding proper gowning technique. The gowning requirements are specific for each area. Magnetic key card access to work areas is based on training requirements.

Facility and equipment cleaning is managed per procedures that describe the cleaning and disinfection use, frequency, and methods to be used. The firm uses the following definitions for cleaning and disinfection agents:

- Bactericidal agent: Agent that destroys vegetative bacteria when used in sufficient concentration for a specified contact time.
- Cleaning: Cleaning is a process aimed at removing residues, particles or other substances from surfaces and equipment. In the context of cleanroom cleaning and disinfection, cleaning is performed primarily to remove substances that could

interfere with the disinfection process. Cleaning agents may include detergent and have solubilizing and surface-active properties that enable them to remove interfering substances.

- Disinfectant: A chemical or physical agent that destroys or removes microorganisms. The agent may be bactericidal, fungicidal, sporicidal depending on the intended use and the associated qualification.
- Disinfection: Process using a disinfectant to destroy microorganisms on a surface
- Fungicidal agent: Agent that destroys yeasts and mold when used in sufficient concentration for a specified contact time.
- Sporicidal agent: Agent that destroys bacterial and fungal spores when used in sufficient concentration for a specified contact time.
- Sterilization: Process which destroys all forms of microbial life including fungi, viruses, and all forms of bacteria and their spores with at least (b) (4) reductions within a specified exposure time.

Equipment is cleaned via (b) (4)) method and use (b) (4) detergent solution for cleaning agents. Parts washers used to clean small parts and glassware use (b) (4) cleaning agents. (b) (4)

(b) (4)

The following agents are used to clean and disinfect non-product contact surfaces:

- (b) (4)

Facility cleaning and disinfection is performed according to a defined frequencies depending on risk. Routine (b) (4) cleaning and disinfection of (b) (4), working surfaces, equipment surfaces, floors, and MALs is performed using bactericidal agents. (b) (4) cleaning and disinfection of floors, walls, ceilings, vertical surfaces, and working surfaces is performed using bactericidal, fungicidal, and sporicidal agents. Intensive (b) (4) cleaning and disinfection of floors, walls, ceilings, vertical surfaces, and working surfaces is performed using detergent, bactericidal, fungicidal, and sporicidal agents.

Product changeover procedures are performed before and after a manufacturing operation. Cleaning requirements are verified before an area is used for manufacturing.

Reviewer's comment: In amendment 125819/0.10, GSK confirmed that the MenA, C, W, and Y manufacture, CRM manufacture, and conjugate manufacture is performed on the (b) (4) floor using the same manufacturing areas,

critical support equipment and critical utilities as registered for Menveo (BL 125300). Additionally, OMV is manufactured on the (b) (4) using the same manufacturing areas, critical support equipment, and critical utilities as registered for Bexsero (BL 125546).

Computer Systems

(b) (4) utilizes a Building Automation System (BAS), Process Automations Systems (PAS) for process equipment control, and (b) (4). The systems are validated for their intended use, per 21 CFR Part 11 and EU Annex 11. The BAS controls the HVAC systems, monitors environmental conditions, and generates alarms for environmental parameters at the facility. In (b) (4), the (b) (4) PAS systems are PAS (b) (4) and PAS (b) (4). The systems manage process equipment. PAS functions include batch recipe management, equipment alarm management, report generation, data acquisition, and user operation. (b) (4) is used to manage the process support equipment for product transfer, cleaning, steaming, and associated alarms management. All systems limit access via password/user ID authentication to prevent unauthorized access and log user inputs to maintain traceability.

Reviewer's comment: *In amendment 125819/0.10, GSK confirmed that the MenA, C, W, and Y manufacture, CRM manufacture, and conjugate manufacture is performed on the (b) (4) floor using the same manufacturing areas, critical support equipment and critical utilities as registered for Menveo (BL 125300). Additionally, OMV is manufactured on the (b) (4) using the same manufacturing areas, critical support equipment, and critical utilities as registered for Bexsero (BL 125546). The computer systems did not require re-review to support this product application.*

Building (b) (4) 1

In Section 3.2.A.1 Facilities and Equipment – Building (b) (4) – Chapter 1 – Facility Description, GSK provided a list of shared and dedicated areas, flow charts of manufacturing unit operations, and links to facility drawings.

(b) (4) is a (b) (4) building that includes a (b) (4) floor (Level (b) (4) (Level (b) (4), and a (b) (4) (Level (b) (4) Levels (b) (4) is the manufacturing floor, which is supported by technical areas located on Levels (b) (4) is dedicated to the manufacture of vaccines and adjuvants. In addition to the MenB Liquid component, (b) (4) also formulates and fills Bexsero, (b) (4)

Production areas are ISO (b) (4) (Grade (b) (4) and ISO (b) (4) (Grade (b) (4) and include the following:

- (b) (4)

- (b) (4)

All rooms are shared for manufacturing.

Personnel change into the appropriate attire (Grade (b) (4) gowning) in the changing rooms on the (b) (4). The changing rooms (b) (4)

Reviewer's comment: In amendment 125819/0.10, GSK confirmed that the MenB Liquid component manufacture is performed using the same manufacturing areas, product contact equipment, critical support equipment and critical utilities as registered for Bexsero (BL 125546).

The contamination and cross-contamination controls employed at (b) (4) are the same as (b) (4) in terms of overall approach (facility design, equipment design, and containment procedures). The non-product contact disinfectants and cleaning and disinfection frequencies are the same. The line clearance and changeover procedures are also the same. The only differences are related to equipment cleaning which is due to the use of different equipment in each building.

The computer systems used in (b) (4) are a BAS (b) (4) for automation of HVAC and utilities and a PAS (b) (4) for process automation. These systems were validated in 2012-2013 and unchanged since the initial Bexsero approval (January 23, 2015).

(b) (4) Equipment




In Section 3.2.A.1 Facilities and Equipment – Building (b) (4) – Chapter 2 – Equipment, Table 2, the firm listed dedicated, shared, and single use types of equipment and materials used in (b) (4).

Dedicated mobile equipment are (b) (4)

. Shared mobile equipment are (b) (4)

Single use materials/equipment are (b) (4)

(b) (4)




Reviewer's comment: In amendment 125819/0.10, GSK confirmed that MenB Liquid manufacture is performed on the (b) (4) floor using the same manufacturing areas, product contact equipment, critical support equipment and critical utilities as registered for Bexsero (BL 125546).

(b) (4) HVAC Systems

In Section 3.2.A.1 Facilities and Equipment – Building (b) (4) – Chapter 3 – HVAC, the firm provided information regarding the HVAC systems at (b) (4). The facility utilizes AHUs that supply air to the manufacturing areas. (b) (4) manufacturing areas, corridors, and airlocks are classified Grade (b) (4) (Grade (b) (4) air quality), with a Grade (b) (4) in the Grade (b) (4) formulation room. (b) (4) has no Grade (b) (4) areas. HVAC system control, including air flow, pressure, temperature, humidity, monitoring, and alarms are managed via a BAS.

The MenB manufacturing areas are supported by AHUs (b) (4)



(b) (4)

Environmental Monitoring

The firm provided a list of past environmental monitoring validations (EMPQs) in Section 3.2.A.1 Facilities and Equipment – Building (b) (4) – Chapter 3 – HVAC, Table 9. Manufacturing and support areas are monitored for non-viable air particles, active air, passive air, and surfaces. The following acceptance criteria are used (based on the ISO (b) (4) Standard):

(b) (4)

Routine monitoring is conducted according to area classification. The Grade (b) (4)

Reviewer's comment: In amendment 125819/0.10, GSK confirmed that the manufacturing areas, critical support equipment, and critical utilities are the same as those registered for Bexsero (BL 125546). The HVAC system qualifications and EMPQs were previously reviewed under the Bexsero (BLA 125546/0) original application and/or supplements.

(b) (4) **Water Systems**

(b) (4) produces PW and WFI from (b) (4) water supplied by Building (b) (4). (b) (4) water from (b) (4) to produce PW. The PW is distributed to (b) (4) CS generator (b) (4). WFI is produced by WFI generator (b) (4). The WFI storage and distribution system (b) (4).

The CS generator (b) (4) supplies the CS distribution systems, which in turn supplies the CS POUs. A diagram of the (b) (4) water system was provided in Section 3.2.A.1 Facilities and Equipment – Building (b) (4) – Chapter 4 – Water Systems, Figure 1.

Routine monitoring of the WFI system for (b) (4), whereby the sampling sites are sampled at least (b) (4) on a rotating basis to cover all sample sites. Routine monitoring of the WFI system for (b) (4).

The WFI system is tested for (b) (4). The PW system is tested (b) (4). The following WFI acceptance criteria are used:

(b) (4)

Reviewer's comment: The (b) (4) water system was previously reviewed under the Bexsero (BLA 125546/0) original application and/or supplements. In amendment 125819/0.10, GSK confirmed that the existing systems used to manufacture Bexsero are also used to manufacture the MenB Liquid component.

(b) (4) Process Gases

Process gas information was provided in Section 3.2.A.1 Facilities and Equipment – Building (b) (4) – Chapter 5 – Pure Steam, Compressed Air, and Nitrogen Systems. (b) (4) process gases consist of CS, compressed air, and nitrogen. CS is used for (b) (4). CAP is used to (b) (4). Nitrogen is used during (b) (4).

Routine monitoring of the CS system is performed (b) (4) by sampling throughout each (b) (4) to cover all sample points. The following acceptance criteria are used:

(b) (4)

Routine monitoring of the CAP system is performed (b) (4) by sampling throughout each (b) (4) to cover all sample points. The following acceptance criteria are used:

(b) (4)

Routine monitoring of the Nitrogen system is performed (b) (4) by sampling throughout each (b) (4) to cover all sample points. The following acceptance criteria are used:

(b) (4)

Reviewer's comment: The (b) (4) gas systems were previously reviewed under the Bexsero (BLA 125546/0) original application and/or supplements. In amendment 125819/0.10, GSK confirmed that the existing systems used previously for Bexsero are also used for the MenB Liquid component.

3.2.A.1 Facilities and Equipment (b) (4)

MenABCWY vaccine components are manufactured in buildings (b) (4) at the GSK facility in (b) (4) is a multi-product facility used to formulate, fill, lyophilize, and inspect the MenACWY Lyo component. The information provided is organized according to each building (i.e., (b) (4)).

Reviewer's comment: In amendment 125819/0.18, GSK confirmed that the validated manual cleaning, automatic cleaning, and sterilization procedures are currently used without any changes. A Periodic Validation Review (PVR) of the manual cleaning, automatic cleaning and sterilization process is carried out on each system to determine if a requalification/revalidation is necessary.

Building (b) (4)

In Section 3.2.A.1 Facilities and Equipment – Building (b) (4) – Chapter 1 – Facility Description, the firm provided a list of vaccine and adjuvant products formulated in building (b) (4), which include US licensed vaccines (b) (4). The Section also includes a list of shared workspaces, product flow diagram, and links to facility drawings.

The MenACWY final (b) (4) process flow consists of (b) (4) addition in the (b) (4), and storage at 2 – 8°C. These activities are conducted in ISO (b) (4) classified areas.

The following product-contact equipment is listed in Section 3.2.A.1 Facilities and Equipment – Building (b) (4) – Chapter 2 – Equipment, Table 1:

- (b) (4)

(b) (4)


The (b) (4) process allows for (b) (4) to occur in a (b) (4)

Small Parts


Product-contact re-usable small materials include (b) (4)

Singe-Use Materials

All single-use items, such as (b) (4)



(b) (4)





Support Equipment

The following support equipment are used in building (b) (4):

(b) (4)

Cleaning Validation

(b) (4)



(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

The routine monitoring plan was provided in Section 3.2.A.1 Facilities and Equipment – Building (b) (4) – Chapter 3 – HVAC Systems, Table 8. The ISO (b) (4) rooms are monitored (b) (4) during operations, and (b) (4) at the end of activities.

Reviewer's comment: The information was reviewed under reviewed under BLA STN 125775/0 (approved May 3, 2023). The viable, non-viable environmental monitoring is consistent with industry standards (i.e., ISO (b) (4) and (b) (4) .

Building (b) (4)

In Section 3.2.A.1 Facilities and Equipment – Building (b) (4) – Chapter 1 – Facility Description the firm provided a list of vaccine and adjuvant products filled in building (b) (4), which include US licensed vaccines (b) (4). The Section also includes a list of shared workspaces, flow diagrams, and links to facility drawings.

Building (b) (4) consists of the following areas:

- (b) (4)


The MenACWY Lyo component product flow in building (b) (4) consists of the following production Level (b) (4) rooms and process steps:

- (b) (4)

(b) (4)




(b) (4) Equipment

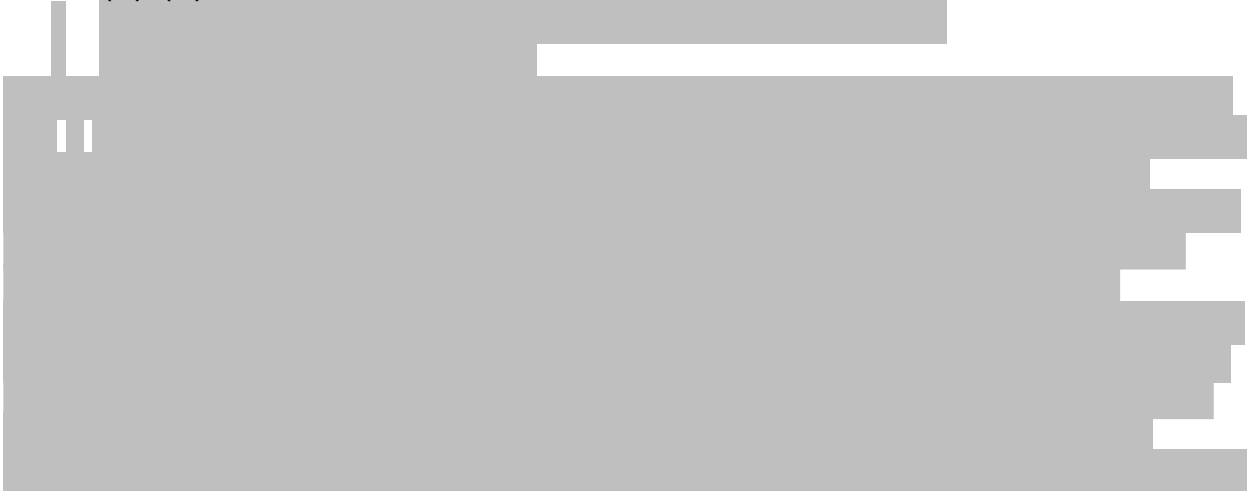
Equipment information was provided in Section 3.2.A.1 Facilities and Equipment – Building (b) (4) – Chapter 2 – Equipment. Building (b) (4) product-contact equipment dedicated to (b) (4)



Reviewer's comment: *The information provided regarding the shared filling line equipment, mobile process equipment, and support equipment is the same as the information provided under BLA STN 125775/0 (approved May 3, 2023). The shared equipment validation reports are the same except for (b) (4) validation report VA-0000412164 (covered in the (b) (4) decontamination section below).*

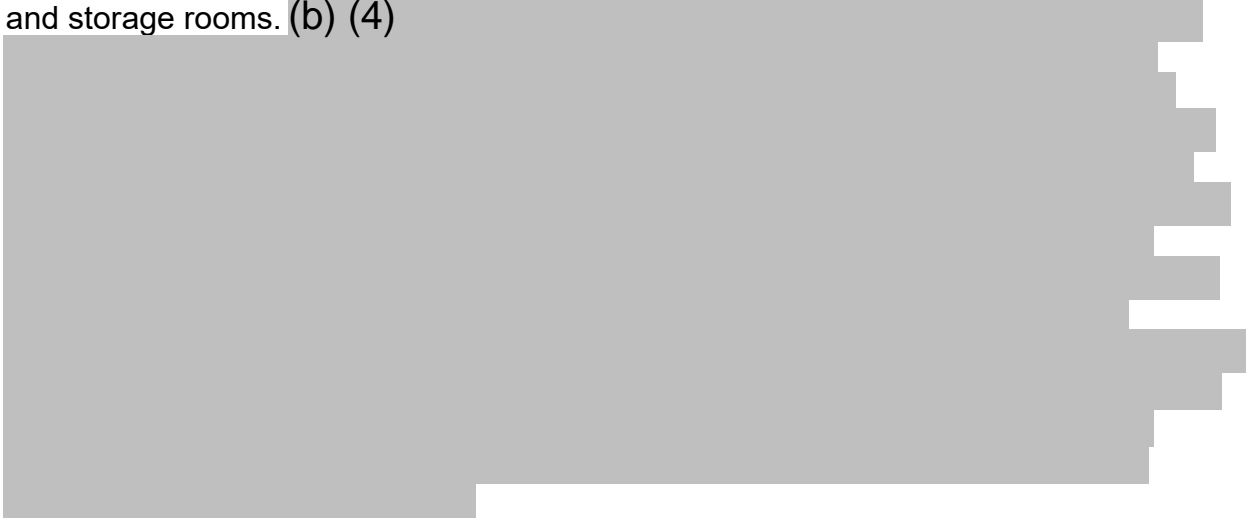
(b) (4)



- (b) (4)
- 
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(b) (4) HVAC

In Section 3.2.A.1 Facilities and Equipment – Building (b) (4) – Chapter 3 – HVAC, the firm provided (b) (4) HVAC systems information. Building (b) (4) areas are serviced by segregated AHUs that supply air to the manufacturing rooms, airlocks (PALs/MALs), and storage rooms. (b) (4)




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The HVAC system dedicated to the (b) (4)



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(b) (4)



Manufacturing and support areas are monitored for non-viable air particles, active air, passive air, and surfaces. The following acceptance criteria are used (based on the ISO (b) (4) Standard):

(b) (4)

(b) (4)

The routine monitoring plan was provided in Section 3.2.A.1 Facilities and Equipment – Building (b) (4) – Chapter 3 – HVAC Systems, Table 8. The (b) (4) are monitored (b) (4). ISO^{(b) (4)} areas are monitored (b) (4) for each shift or batch during operations, (b) (4) of activities, and (b) (4) for each operator. ISO^{(b) (4)} areas are monitored (b) (4) and (b) (4) during operations, and (b) (4) of activities.

Reviewer's comment: The information was reviewed under reviewed under BLA STN 125775/0 (approved May 3, 2023). The viable, non-viable environmental monitoring is consistent with industry standards (i.e., ISO (b) (4) and (b) (4)).

Control of Contamination and Cross-Contamination

Contamination and cross-contamination control information was provided in Section 3.2.A.1 Facilities and Equipment – Building (b) (4) – Chapter 6 – Contamination & Cross Contamination Control. Control of contamination and cross-contamination is achieved by way of the following:

- (b) (4)

Facility Design

The buildings used are of suitable size, construction, and design to facilitate cleaning, maintenance, and proper operations. The facility is designed to contain product intermediates and solutions in production (b) (4) and process (b) (4) by using closed systems. Additional containment is achieved by maintaining (b) (4) between rooms. MenACWY filling and (b) (4) operations are performed in ISO (b) (4). The (b) (4).

Production rooms are designed with surfaces that are durable, smooth, and easily cleanable. Interior surfaces must be free from cracks and open joints and maintained in a good state of repair. Light fixtures, windows, doors, and control panels are flush, minimizing potential for dust build-up. The building design is based on the principle of physical and operational segregation to prevent cross-contamination from other facilities and between production campaigns.

The facility is designed with the following features:

- Separate access for personnel and raw materials,
- Separate exit for product,
- Use of magnetic key cards for access of personnel to their respective manufacturing area,
- Utilities dedicated to the manufacturing area,
- HVAC units dedicated to the manufacturing area,
- Multiproduct (b) (4) and product contact material with validated cleaning methods,
- Dedicated manufacturing support areas (i.e., (b) (4) , ambient storage, and cold storage).

Equipment Design

Production equipment was purchased from proprietary suppliers with expertise in equipment design and manufacture in compliance with GlaxoSmithKline (GSK) engineering and user requirements. The (b) (4) to provide for smooth surfaces free of

crevices that may promote bacterial growth. (b) (4)

The equipment used in the aseptic areas are designed and installed to permit ease of cleaning and to minimize turbulence of the unidirectional air flow.

HVAC

The facilities are serviced by segregated AHUs to supply the air to the process rooms, personnel and material airlocks, and storage rooms. Air pressure differentials are maintained between manufacturing areas. Segregation and containment are aided by the use of airlocks. Additional HVAC information is in the HVAC section.

Cleaning, Disinfection, and Decontamination

Facility and equipment cleaning is conducted according to established procedures.

Product-contact equipment and re-usable materials are (b) (4)

, as applicable. Indirect product-contact equipment (b) (4)

are cleaned via (b) (4). Single use materials are cleaned (b) (4)

. Single use materials are

discarded after use to avoid cross-contamination. Product-contact equipment or

materials are cleaned within (b) (4) after use (b) (4).

For product-contact equipment or materials:

- (b) (4)

The following cleaning and disinfection/decontamination agents used for non-product contact surfaces:

- (b) (4)

The firm provided disinfectant efficacy studies listed in Table 1 of Section 3.2.A.1 Facilities and Equipment – Building (b) (4) – Chapter 6 – Contamination & Cross-Contamination Control.

The validations consisted of laboratory qualification of the disinfection agents and field qualifications. The specifications are listed as follows:

- (b) (4)

The studies were performed on materials including (b) (4)

Reviewer's comment: *The disinfectant efficacy studies provided are the same as the studies reviewed and approved under BLA 125775/0 (approved May 3, 2023). The studies provided were performed from 2008 – 2018, with the majority performed from 2016 – 2018. Based on communication with the firm (amendment 125819/0.18), the facility information provided in the submission is current.*


If required, materials and equipment are sterilized (b) (4) cleaning. Vials are (b) (4) filling. Sterilization is performed by (b) (4)

The following cleaning and disinfection frequencies are used:

- (b) (4)

Bactericidal agents are validated to reduce vegetative bacteria by at least (b) (4) when used in sufficient concentration for a specified contact time. Fungicidal agents are validated to reduce yeast by at least (b) (4) and mold spores by at least (b) (4) when used in sufficient concentration for a specified contact time. Sporocidal agents are validated to reduce bacterial and fungal spores by at least (b) (4) when used in sufficient concentration for a specified contact time. Virucidal agents are validated to destroy virus when used in sufficient concentration for a specified contact time.

(b) (4)



Reviewer's comments: The log reduction limits comply with (b) (4) for vegetative and spore-forming microorganisms. The viruses used for testing are representative of the viruses in the attenuated viral vaccines manufactured in building (b) (4). The facility cleaning, and disinfection program appears acceptable.

Personnel Controls

All operators have been specifically trained to their assigned job functions, in aseptic processing techniques and Good Manufacturing Practice (GMP) requirements; training is documented. All operators have been qualified for proper gowning technique. Prior to entering the aseptic areas, all operators dress in sterile garments in designated personnel air locks. Prior to touching any equipment or prior to introducing any material under ISO (b) (4), operators (b) (4) with a validated disinfection solution. When working in aseptic areas, operator's gloved hands are monitored to ensure good aseptic practices. A gowning test is also performed on each operator working in the aseptic areas. For (b) (4) manipulations, operators are dressed in production garments (depending on the room classification), wearing sterile gloves. In aseptic areas, operators wear sterile gowning (with hood) and goggles, fully covering their head and neck area: this minimizes the probability of product contamination by operator. Dedicated operators working in ISO (b) (4) or ISO (b) (4) are qualified via aseptic process simulation.

Facility Flows

Prior to entering the aseptic areas, all materials are (b) (4). When required, the (b) (4) materials entering these rooms are (b) (4) in the material air lock (MAL). The (b) (4) materials used under (b) (4) are discarded prior to entering (b) (4).

Waste materials and direct product-contact materials coming from rooms containing virus are decontaminated (b) (4) the process area. All liquid waste coming from rooms containing live attenuated virus is decontaminated (b) (4) to the site effluent system. Wastes are removed from the facility according to GSK procedures.

Personnel gown into clean room garments in rooms (b) (4). Personnel use corridor (b) (4)

Reviewer's comments: The personnel, material, and waste flow information appear acceptable.

Line Clearance and Changeover Procedures

Product changeover, equipment, cleaning, and room clearance procedures are in place to avoid mix-ups and cross-contamination. Product is identified at each stage of the production process to avoid mix-ups and ensure traceability. GSK utilizes validated cleaning and changeover procedures, including manual decontamination of the (b) (4) following live attenuated virus vaccine campaigns. The decontamination agents used are validated to completely inactivate viruses manufactured on line (b) (4) (i.e., (b) (4)). Validation of the changeover process was provided in summary report VA-0000389824-PQ&PV.

The validation consisted of (b) (4) after the cleaning, disinfection, and decontamination steps. (b) (4) The following validity and acceptance criteria were used:

- (b) (4)

All acceptance and validity criteria were met. No deviations were reported.

(b) (4)

(b) (4)

Reviewer's comments: The sampling locations appear acceptable since the represent places where spillage risk is present or places frequent operator movement. The changeover procedure, including disinfection, appears to prevent virus contamination (b) (4) from the (b) (4). In amendment STN 125819/0.18, GSK stated that a manual decontamination of the (b) (4) is performed with (b) (4). According to provided disinfectant efficacy studies, (b) (4) alone achieves complete (b) (4).

The evidence provided in the changeover validation and disinfectant efficacy studies supports virus inactivation of the (b) (4). In amendment 125819/0.32, GSK provided the product changeover SOP (9000004291) and filling line (b) (4) decontamination checklist (9000042124). The procedures require (b) (4).

The checklist appears to be comprehensive and includes example images for each step and clearly defined (b) (4) locations for each area. Based on the information provided, the filling line (b) (4) line clearance and product changeover practices appear acceptable.

Building (b) (4)

In Section 3.2.A.1 Facilities and Equipment – Building (b) (4)– Chapter 1 – Facility Description, Table 1, the firm provided a list of vaccine and adjuvant products processed in building (b) (4), which include US licensed vaccines (b) (4) filled on the same filling line using the same container closure. The section also includes a list of shared workspaces, product flow diagram, and links to facility drawings.

(b) (4) is a (b) (4) building consisting of labelling, packaging, and visual inspection areas on the (b) (4) floor and changing rooms, offices, and access corridors on the (b) (4) floor. MenACWY Lyo is processed using room (b) (4) for (b) (4).

(b) (4)

Equipment used to process MenACWY Lyo FC consists of (b) (4)

The equipment has been previously validated and submitted to the Agency and approved for use on lyophilized products filled in (b) (4). Information was submitted under PAS STN (b) (4) and approved on (b) (4). The (b) (4) was submitted, along the (b) (4) under CBE-30 STN (b) (4) and approved on (b) (4). The (b) (4) equipment

was submitted under CBE-30 STN (b) (4)

(b) (4)

(b) (4)

Reviewer's comment: The results of the PPQ show that the (b) (4) visual inspection processes consistently conform to AQL Level (b) (4) limits. At least (b) (4) batches were processed within limits using the (b) (4) method (b) (4). Along with the firm's history of performing visual inspection of lyophilized products at this facility using the same or equivalent container closure systems, the information provided appears acceptable.

3.2.A.1 Facilities and Equipment (b) (4)

(b) (4)



- (b) (4)

Equipment

Equipment information was provided in Section 3.2.A.1 Facilities and Equipment – (b) (4) – Chapter 2 – Equipment. The following tables list the product-contact equipment is according to building number at the (b) (4) Facility. In addition to the re-usable equipment listed below, single-use material includes (b) (4)

(b) (4)

(b) (4)

(b) (4)

Shared equipment in building (b) (4) used for filling of (b) (4) consists of filling (b) (4)

Reviewer's comment: *The equipment is pre-existing and used to manufacture the same recombinant proteins for US-licensed MenB vaccine, Bexsero. Thus, further evaluation of the equipment qualification is not needed for this product application.*

Cold Rooms

Cold room qualification reports were provided in Tables 11 – 14 in Section 3.2.A.1 Facilities and Equipment – (b) (4) – Chapter 2 – Equipment.

Reviewer's comment: *The cold rooms are pre-existing and used to manufacture the same recombinant proteins for Bexsero.*

Equipment Cleaning

The equipment cleaning procedure is described in general in Section 3.2.A.1 Facilities and Equipment – (b) (4) – Chapter 2 – Equipment. (b) (4)

(b) (4)

(b) (4) equipment is validated according to a matrix approach, whereas all (b) (4) /purification equipment cleaning is validated in totality. A list of cleaning validation studies was provided in Table 15 in Section 3.2.A.1 Facilities and Equipment – (b) (4) – Chapter 2 – Equipment.

The cleaning process is evaluated (b) (4) based on the impact of changes and quality events (i.e., deviations) or CAPAs.

(b) (4)

Reviewer's comment: The (b) (4) acceptance criteria appear acceptable for upstream equipment. The same equipment, cleaned according to the same procedures, is used to manufacture the same recombinant proteins for Bexsero.

Equipment Sterilization/Sanitization

Equipment used in (b) (4) purification steps in (b) (4)

(b) (4) are re-qualified on an (b) (4) basis (every (b) (4)). The re-qualifications are performed with maximum (b) (4) as a worst-case scenario and at least (b) (4) runs are executed. (b) (4) is included. The (b) (4) qualification reports were provided in Tables 19 – 25 in Section 3.2.A.1 Facilities and Equipment – (b) (4) – Chapter 2 – Equipment.

Reviewer's comment: The (b) (4) used for the MenB recombinant proteins are previously qualified and none of the (b) (4) are newly installed. The same (b) (4) were previously approved for the manufacture of the same recombinant proteins for Bexsero.

(b) (4) HVAC

HVAC information was provided in Section 3.2.A.1 Facilities and Equipment – (b) (4) – Chapter 3 – HVAC Systems. Room classifications are based on (b) (4) and ISO (b) (4). The room classification limits are summarized below:

(b) (4)

(b) (4)

(b) (4)

GSK provided a list of each HVAC system in each building in Table 19. Facility drawings of the HVAC system was also provided in Section 3.2.A.1 Facilities and Equipment – (b) (4) – Chapter 3 – HVAC Drawings. (b) (4) is covered by air handling units (AHUs) (b) (4) preparation areas are covered by AHU (b) (4) areas are covered by AHUs (b) (4) is covered by AHUs (b) (4). The most recent holistic requalifications were performed in 2019 for (b) (4) AHUs and in 2021 for (b) (4) AHUs. Environmental trend reports are generated (b) (4) and (b) (4) for each HVAC system.

Novartis Kundl EMPQ

EMPQ information was provided in Section 3.2.A.1 Facilities and Equipment – (b) (4) – Chapter 3 – HVAC Systems. The limits for EM and EMPQ were provided in Table 6 (summarized below).

(b) (4)

(b) (4)

Reviewer's comment: The HVAC system at (b) (4) ensure production and support areas are in accordance with industry standards for cleanrooms. The same rooms used to manufacture the MenB recombinant proteins are used to manufacture the same recombinant proteins for Bexsero.

Water System

Water system information was provided in Section 3.2.A.1 Facilities and Equipment – (b) (4) – Chapter 4 – Water Systems. There is a purified water (PW) and water for injection (WFI) system at the (b) (4) facility. The source water for the PW system is potable water. PW is used for equipment cleaning, production room cleaning, (b) (4) processes, and as the source for WFI and clean steam. WFI is used for equipment cleaning, cleaning of production rooms, disinfectant preparation, and downstream processes.

The buildings (b) (4) are supplied with (b) (4) PW from the (b) (4)

PW limits:

- (b) (4)

WFI limits:

- (b) (4)

Reviewer's comment: The water system testing at (b) (4) is validated and the testing and acceptance criteria are in accordance with industry standards. The system is also used to manufacture the same recombinant proteins for Bexsero. The information provided appears acceptable.

Process Gas Systems

Process gas systems information was provided in Section 3.2.A.1 Facilities and Equipment – (b) (4) – Chapter 5 – Process Gas Systems. The following critical gas systems are used in buildings (b) (4):

- Pure steam (PS): mainly used for the (b) (4)
- Plant steam: mainly used for the (b) (4)
- Compressed air for process (CAP): used for (b) (4)
- Nitrogen: used as (b) (4)

Pure/Clean Steam System

The pure/clean steam for the respective buildings is produced in (b) (4) clean steam generators, (b) (4)

- (b) (4)

Reviewer's comment: The process gas systems used at (b) (4) are validated. The testing and acceptance criteria are in accordance with industry standards. The systems are also used to manufacture the same recombinant proteins for Bexsero. The information provided appears acceptable.

Contamination and Cross-Contamination Control

Contamination and cross-contamination control information was provided in Section 3.2.A.1 Facilities and Equipment – (b) (4) – Chapter 6 – Contamination/Cross Contamination Control. Containment and control of cross-contamination is achieved in various ways, including:

- Facility Design
- Equipment Design
- HVAC and Environmental Monitoring
- Facility Cleaning and Disinfectant Agents
- Personnel Controls/Gowning Requirements
- Facility Flows
- Line Clearance and Changeover Procedures

Facility Design

The buildings used are of suitable size, construction, and design to facilitate cleaning, maintenance, and proper operations. The facility design philosophy is to attain a primary containment in the (b) (4)

Production rooms are designed with surfaces that are durable, smooth, and easily cleanable. Interior surfaces must be free from cracks and open joints and maintained in a good state of repair. Light fixtures, windows, doors, and control panels are flush, minimizing potential for dust build-up. The building design is based on the principle of physical and operational segregation to prevent cross-contamination from other facilities and between production campaigns.

Equipment Design

Production equipment was purchased from suppliers with expertise in equipment design and manufacture, in compliance with (b) (4) engineering and use requirements. Internal finishes on equipment are (b) (4) to provide for smooth surfaces free of crevices that may promote bacterial growth. (b) (4)

Process equipment systems were designed for pharmaceutical purposes (i.e., (b) (4)). Process equipment is (b) (4) to ensure effective cleaning and sterilization/sanitization can be performed. Product contact surfaces are designed with material and surface finishes that assure cleanability. Systems are equipped with (b) (4)

(b) (4)

Equipment is qualified and/or calibrated.

HVAC and Environmental Monitoring

The facilities are serviced by segregated AHUs to supply the air to the process rooms, personnel and material airlocks and storage rooms. Special precautions and working instructions are employed for areas in which (b) (4)

Environmental action and alert levels are established for all classified areas. EM frequencies are based process risk and area classification, with higher risk processes and higher areas classifications being monitored more frequently. Microbiological trend reporting is performed on a (b) (4).

Facility Cleaning and Disinfectant Agents

A cleaning and disinfection program is in place for all classified clean room areas. Cleaning and disinfection of room surfaces, and equipment exterior surfaces are performed in accordance with SOPs. Qualified disinfectant agents are used for disinfection of various surfaces of the clean rooms. For each area, the disinfectant is regularly changed. Qualification of the disinfectant solutions is performed on different surfaces using (b) (4) qualification tests: a (b) (4) test and a (b) (4) test. Requirements (b) (4) test:

- (b) (4)

All used disinfectant solutions must fulfill the given requirements.

- Agents for cleaning, disinfection and decontamination of product contact equipment and materials:
 - (b) (4)
- Agents for cleaning, disinfection and decontamination of non-product contact equipment, surfaces, and materials:
 - (b) (4)

Personnel Controls

All operators have been specifically trained to their assigned job functions, in aseptic processing techniques and GMP requirements, and training is documented. All operators have been qualified for proper gowning technique. Gowning and operator

behaviors are governed by established procedures. Areas that are classified a higher status have more stringent gowning requirements. Clothing instructions are in place for personnel as well as for visitors. Access to manufacturing areas is limited to personnel with, or in the company of staff with documented training. Access is controlled via personnel badges and an automated system.

Facility Flows

Materials are disinfected/sanitized before entering Grade (b) (4) areas. The production (b) (4) is categorized as biosafety level (b) (4). Its handling is fully compliant with (b) (4) requirements as specified by the strict local (i.e. (b) (4)) regulations and laws. Exhaust gasses from these areas is treated appropriately to (b) (4) regulations. All waste streams that are potentially containing the production (b) (4) are contained and (b) (4) within the (b) (4) wastewater treatment plant. (b) (4) is typically performed (b) (4) but batch (b) (4) may be used when necessary.

Line Clearance and Changeover Procedures

Product changeover, equipment, cleaning, and room clearance procedures are in place to avoid mix-ups and cross-contamination. Product is adequately identified at each stage of the production process to avoid mix-ups and ensure full traceability. (b) (4) utilizes validated cleaning and changeover procedures, including testing for residues if appropriate, to control transfer of (b) (4) and product residues between runs as well as between products. Changeover procedures include (b) (4) testing in addition to validated cleaning procedures. Depending on the product, product specific assays may be performed on (b) (4) from specified surfaces to verify product removal. Additionally, all (b) (4) are replaced with every product change.

Reviewer's comment: *The contamination and cross-contamination controls appear acceptable in terms of facility/equipment design, cleaning, HVAC/EM, gowning, facility flows, and clearance/changeover. The same facility, equipment, systems, procedures, and manufacturing rooms are used to manufacture the same recombinant proteins for Bexsero. The information provided appears acceptable.*

Computer Systems

Computer systems information was provided in Section 3.2.A.1 Facilities and Equipment – (b) (4) – Chapter 7 – Computer Systems. Automated process systems are used at the (b) (4) site to monitor and control process equipment. All process automation systems used for MenB recombinant proteins are in a qualified state.

Reviewer's comment: *The computer systems used for MenB recombinant protein manufacture are previously qualified. The same computer systems were previously approved for the manufacture of the same recombinant proteins for Bexsero.*


3.2.A.1 Facilities and Equipment (b) (4)

(b) (4) building (b) (4) facility information was provided in Section 3.2.A.1 Facilities and Equipment – Building (b) (4) – Chapter 1 – Facility Description, Drawings, and Chapter 2 – Equipment. (b) (4) GlaxoSmithKline Vaccines (referred to as GSK (b) (4) Building (b) (4) is a multi-product facility dedicated to visual inspection, labeling and packaging of vaccines, adjuvants, and diluents, located in (b) (4). The (b) (4) facility will be used for the labeling and secondary packaging of the MenACWY Lyophilized component in vials, the MenB Liquid component in pre-filled syringes, and the finished MenABCWY vaccine kit. The facility is currently approved for labeling, packaging, and storage of GSK vaccines including recombinant vaccines, purified inactivated vaccines, polysaccharide vaccines, combination vaccines, adjuvants, attenuated viral vaccines, and WFI diluent.

(b) (4)



Figure 1 in Section 3.2.A.1 Facilities and Equipment – Building (b) (4) – Chapter 1 – Facility Description shows the packaging flow. Steps consist of (b) (4)



The facility has defined flows for personnel, materials, and waste. Drawings were provided to illustrate facility flows.

All equipment at the (b) (4) facility is non-product contact. Equipment includes (b) (4)



For vials, labels are overprinted with lot number and expiry date and then affixed to the vial. For syringes, a plunger rod is screwed on the stopper of each syringe, which is then labelled with a self-adhesive label, overprinted with lot number and expiry date. The labeled vial and syringes are then introduced into a grouping carton (containing 10 vials of MenACWY antigen and 10 syringes of MenB antigen per box) and simultaneously with a product information insert. The filled grouping carton is identified

with lot number, expiry date. Grouping cartons are loaded into grouping boxes, which are identified, palletized, and stored at 2 – 8°C until release.

Reviewer's comment: *The proposed processing and support areas used for MenABCWY vaccine labeling and packaging activities are used for FDA licensed drugs including (b) (4)*

. Relevant facility and equipment information was previously reviewed under the associated BLs. The information provided appears acceptable.

3.2.R Regional Information Combination Products

The MenB Liquid PFS and MenABCWY Lyo Vial vaccine components are registered as a combination product in the MenABCWY Vaccine under the proposed trade name Penmenvy. GSK takes a streamlined approach to comply with the current good manufacturing practice (cGMP) requirements with the overarching quality systems in accordance with the drug and biologics cGMPs and integration of the specific device Quality System Regulation (QSR) provisions that include Management Responsibility (21 CFR 820.20), Design Controls (21 CFR 820.30), Purchasing Controls (21 CFR 820.50), and Corrective and Preventive Actions (CAPAs, 21 CFR 820.100). Note: Installation and Servicing are not applicable to PFS products. The applicant and license holder maintains responsibility and is the holder of information for the MenABCWY vaccine under the QSR.

Reviewer's comment: *GSK provided summaries to explain how it complies with the device QSR provisions for Management Responsibility, Purchasing Controls, and CAPAs. Regarding management responsibility, 21 CFR 820.20 requires the establishment of a quality policy, adequate organizational structure, periodic management review, quality plan, and quality systems procedures. GSK provided procedures that govern local QMS systems, internal audits, and management reviews. Regarding purchasing controls, 21 CFR 820.50 requires device manufacturers to establish and maintain procedures to evaluate suppliers, contractors, and consultants, and to maintain records of purchasing data. GSK provided procedures that define internal policies for approval of suppliers (raw material and services), management of incoming raw materials, periodic review, and supplier records retention. Regarding CAPAs, 21 CFR 820.100 requires device manufacturers to establish and maintain procedures to implement CAPAs. CAPA procedures should include the conditions under which potential CAPAs are identified, implemented, verified for effectiveness, and documented. GSK provided procedures for CAPA and Change Control management. The quality system documents and procedures GSK provided are internal to the Rosia and (b) (4) sites and were provided in amendment 125819/0.7. The information provided appears to meet the regulatory requirements. In amendment 125819/0.7, GSK noted the cGMP requirements for combination products are applicable to their Rosia and (b) (4) sites. This appears acceptable as these*

are the locations for manufacture of the co-package MenABCWY vaccine – a combination product. Evaluation of the design controls, including risk analyses, is deferred to OVR.