

**CBER BLA Device Review Memorandum – Prefilled Syringe (PFS)**

**BLA STN 125819**

**PENMENY (Meningococcal Group ABCWY Vaccine)**

**Andrea Gray, PhD  
Device Consult Reviewer  
CBER/ORO/DROP/RPB**

1. **BLA#:** STN 125819

2. **APPLICANT NAME**

GlaxoSmithKline Biologicals SA

3. **PRODUCT NAME/PRODUCT TYPE**

- Non-Proprietary/Proper/USAN: Meningococcal Group ABCWY Vaccine
- Proprietary Name: PENMENVY

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

- General Description: Combined Meningococcal Groups A, B, C, W and Y vaccine, also referred to as 'MenABCWY vaccine', consists of two components to be reconstituted before administration: (1) the MenACWY Lyophilized Drug Product (DP) component (also referred to as MenACWY Lyo) as a lyophilized powder in a vial, and (2) the MenB Liquid DP component (also referred to as MenB Liquid) as a suspension for injection in a pre-filled syringe (PFS)
- Route of administration: Intramuscular (IM)
- Indication(s): Active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroup ABCWY.

5. **COMBINATION PRODUCT INFORMATION**

- Type: 9 (both co-packaged and device prefilled with biologic)
- Biologic Constituent(s): Vaccine
- Drug Constituent(s): N/A
- Device Constituent(s): Syringe

6. **MAJOR MILESTONES**

- Filing Meeting: March 23, 2024
- Midcycle Internal Meeting: July 18, 2024
- Late Cycle Internal Meeting: October 31, 2024
- PDUFA Action Date: February 14, 2025

7. **QUALITY REVIEW TEAM**

Reviewer/Affiliation	PFS-Relevant Subject Matter
Marcos Battistel, PhD CBER/OVRR/DBPAP/LBP	Product compatibility, drug product quality attributes including sterility and endotoxin, container closure considerations (e.g., extractables/leachables and toxicological risk assessment, particulates, light protection)
Maria (Floencia) Haurat, PhD CBER/OVRR/DBPAP/LBP	Product compatibility, drug product quality attributes including sterility and endotoxin, container closure considerations (e.g., extractables/leachables and toxicological risk assessment, particulates, light protection)

<b>Reviewer/Affiliation</b>	<b>PFS-Relevant Subject Matter</b>
Jared Greenleaf CBER/OCBQ/DMPQ/MRB1	container closure integrity testing, aseptic processing, sterilization, dehydrogenation, shipping validation (CCIT, plunger stopper movement), some aspects of quality system

## 8. INTRA- & INTER-CENTER CONSULTS

<b>Reviewer/Affiliation</b>	<b>Topic</b>	<b>Agree with consult recommendations? (Yes/No<sup>1</sup>)</b>
Avani Bhalodia CDER/OSE/OMEPRM/DMEPAI	Human factors (ICCR# 00987904)	yes
Amy Chung CDER/OSE/PMS	Human factors (ICCR# 00987904)	yes

## 9. SUBMISSION(S) REVIEWED

<b>Date Received</b>	<b>eCTD Sequence</b>	<b>STN 2<sup>nd</sup> Level</b>	<b>Comments</b>
15 Feb 2024	0001	0	Original submission
3 May 2024	0005	4	Response to CMC/DMPQ IR#3 Comment 5
22 May 2024	0008	7	Additional information including QMS info promised in the response to IR#3 Comment 5
27 Aug 2024	0025	23	Response to device IR#18
14 Nov 2024	0046	44	Updated stability data
04 Dec 2024	0050	48	Response to device IR#33
05 Dec 2024	0051	49	Response to CMC IR#35 regarding packaging configuration
09 Dec 2024	0053	51	Response to CMC IR#34 regarding stability

## 10. RELEVANT REFERENCED REGULATORY SUBMISSIONS

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<b>Submission Type &amp; STN (Center)</b>	<b>Holder</b>	<b>Referenced Information</b>	<b>Letter of Authorization</b>	<b>Comments/Status</b>
DMF (b) (4) (CDER)	(b) (4)	Syringe barrel and plunger stopper	Yes (3.2.R)	No memo required. Leveraged from previous approvals in GSK's portfolio. See Section V of this memo.
DMF (b) (4) (CDER)	(b) (4)	Syringe barrel	Yes (3.2.R)	No memo required. Leveraged from previous approvals in GSK's portfolio. See Section V of this memo.
DMF (b) (4)	(b) (4)	(b) (4) tip cap & (b) (4) plunger stopper	Yes (3.2.R)	No memo required. Leveraged from previous approvals in GSK's portfolio. See Section V of this memo.

## 11. RELEVANT PRIOR INTERACTIONS

This reviewer was not involved in any pre-BLA interactions for this product. However, GSK previously submitted supplements to other BLAs in their vaccine portfolio (listed below) for the same syringe components as part of their (b) (4) syringe harmonization effort and this reviewer was part of the review teams for those products. Some aspects of those reviews is leveraged for this review, as indicated in the review sections below.

- BLA 125546/963 Bexsero
- BLA 103850/5829 Twinrix
- BLA 103475/5721 Havrix
- BLA 103239/5742 Engerix-B
- BLA 103907/6098 Pediarix
- BLA 125106/1540 Boostrix
- BLA 103647/5680 Infanix
- BLA 125260/689 Kinrix
- BLA 125163/678 Flulaval
- BLA 125347/501 Hiberix
- BLA 125127/1133 Fluarix

## 12. REVIEWER SUMMARY AND RECOMMENDATION

### A. EXECUTIVE SUMMARY

GSK submitted BLA 125819 for licensure of their Combined Meningococcal Groups A, B, C, W and Y vaccine, also referred to as 'MenACWY vaccine', consisting of two components to be reconstituted before administration: (1) the MenACWY Lyophilized Drug Product (DP) component (also referred to as MenACWY Lyo) as a lyophilized powder in a vial, and (2) the MenB Liquid DP component (also referred to as MenB Liquid) as a suspension for injection in a pre-filled syringe (PFS). The scope of this review memo includes: PFS description, PFS design verification (including device essential performance, e.g., deliverable volume, (b) (4) verification of device essential performance over the proposed shelf life and after shipping, control strategy to ensure the final combination product meets essential performance requirements, PFS biocompatibility, and compliance with applicable device quality system regulations (design controls regulations (21 CFR 820.30), purchasing control regulations (21 CFR 820.50)). Review of information cross referenced to master files is generally leveraged from previously submitted supplements to other BLAs in GSK's vaccine portfolio for the (b) (4) syringe components as part of their (b) (4) syringe harmonization effort. Based on the information provided in the application, as well as additional information submitted interactively and GSK's commitment to provide confirmatory EPR verification data for product stored for 6 and 48 months as product correspondences, I recommend that the BLA can be approved from a device/combination product perspective.

### B. RECOMMENDATION

#### I. APPROVAL

- In the December 4, 2024, response to IR#33 (sent November 26, 2024), GSK committed to provide Essential Performance Requirements (EPR) testing data using the components of the MenACWY combination product at T6 months and T48 months as it becomes available through Product Correspondences to the MenACWY BLA.

#### II. SIGNATURE BLOCK

Reviewer, Title, Affiliation	Concurrence	Signature and Date
Andrea Gray, PhD Device Reviewer CBER/ORO/DROP/RPB	-	
Cherie Ward-Peralta, MS, RAC Branch Chief CBER/ORO/DROP/RPB	Concur (1/8/2025) (2/10/2025)* (2/14/2025)**	

\*Corrected combination product type from 3 to 9.

\*\*Corrected an amendment number and receipt date in Section 9

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## I. Product Description

### A. Combination Product

Per Module 2.3, Combined Meningococcal Groups A, B, C, W and Y vaccine, also referred to as 'MenABCWY vaccine', consists of two components to be reconstituted before administration:

- (1) the MenACWY Lyophilized Drug Product (DP) component (also referred to as MenACWY Lyo) which is a lyophilized powder in a vial containing four *Neisseria meningitidis* oligosaccharides (MenA, MenC, MenW, MenY), and
- (2) The Meningococcal B component (referred to as MenB Liquid) which is a suspension for injection in a prefilled syringe (PFS) containing the recombinant protein antigens and Outer Membrane Vesicles (OMV) derived from the *Neisseria meningitidis* serogroup B strains.

The MenABCWY reconstituted vaccine (RV) is a ready-to-use liquid preparation for intramuscular administration, obtained by adding the entire content of the MenB Liquid PFS to the MenACWY Lyo vial, to guarantee the delivery of 0.5 mL nominal dose by

withdrawing and administering the entire contents of the reconstituted vaccine from the vial (referred to as "whole content/whole content" administration procedure).

Notably, the MenB Liquid has the same formulation as the approved Bexsero vaccine (STN 125546) with the only difference between Bexsero and the MenB Liquid drug products being a (b) (4)

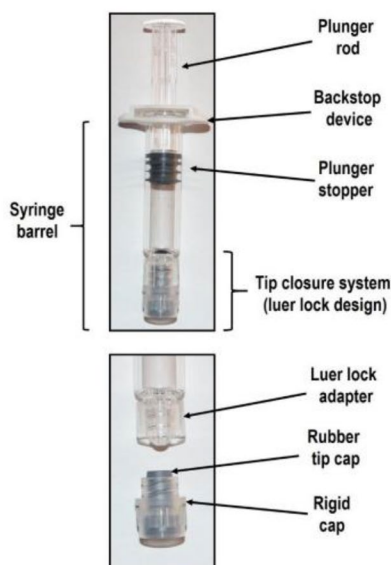
ensure the appropriate administration of the MenABCWY vaccine dose following reconstitution.

## B. Drug/Biologic

Refer to the CMC memo.

## C. Syringe

Figure 1 Overview of typical syringe device constituents



From Module 3.2.P.2.3 "Manufacturing Process Development  
MenB Liquid Specific Development - (b) (4)"

<b>Components and Suppliers</b>	<ul style="list-style-type: none"> <li>Syringe barrel with Luer Lock closure adaptor and rubber tip cap in a rigid cap (b) (4)</li> <li>Plunger stopper ((b) (4)</li> <li>Plunger rod (b) (4), per IR#33 below)</li> </ul>
<b>Connection Type</b>	Luer
<b>Intended Connector(s)</b>	Needle (not provided in product)
<b>Materials of Construction</b>	<p>Barrel: Type (b) (4) Borosilicate glass</p> <p>LLA: polycarbonate</p> <p>Rigid Cap: polypropylene</p>

	Tip Cap: (b) (4) rubber (after (b) (4), not made with natural rubber latex) Plunger stopper: (b) (4) (Bromobutyl type I rubber) Plunger Rod: polystyrene
<b>Dimensions</b>	See Module 3.2.P.7
<b>Syringe Volume</b>	1.25 mL
<b>Fill Volume</b>	(b) (4)
<b>Sterilization Method</b>	Syringe barrel assemblies: (b) (4), validated according to the requirements from ISO (b) (4) Plunger stoppers: (b) (4) Plunger rod: non-sterile
<b>Route of Administration</b>	Intramuscular injection
<b>Administration Site</b>	Injection site necessary for intramuscular injection of vaccines is common knowledge in the healthcare community per <a href="#">ACIP guidelines</a> .
<b>Target Tissue and Depth</b>	Target tissue and depth necessary for intramuscular injection of vaccines is common knowledge in the healthcare community per <a href="#">ACIP guidelines</a> .
<b>Type of Use</b>	Single Use
<b>Storage Conditions and Proposed Expiry</b>	48 months at 2 – 8°C
<b>Intended User(s)</b>	Healthcare professional (HCP)
<b>Intended Use Environment</b>	Clinic
<b>Needle Length, Gauge, Tip Style</b>	Needle specifications necessary for intramuscular injection of vaccines is common knowledge in the healthcare community, per <a href="#">ACIP guidelines</a> .
<b>Markings</b>	n/a
<b>Reuse Durability</b>	n/a
<b>Safety Features</b>	n/a
<b>Automated Functions</b>	n/a

**Information Request (IR)#33.3**
**Date Sent:** November 26, 2024

**Date/Amd/eCTD Sequence Received:** December 4, 2024/48/0050

**IR Comment:** We were not able to find identification of the plunger rod in your submission. For completeness, please clarify the supplier of the plunger rod.



<b>Information Request (IR)#33.3</b>
<b>Date Sent:</b> November 26, 2024
<b>Date/Amd/eCTD Sequence Received:</b> December 4, 2024/48/0050
<b>Applicant Response:</b> The Company clarifies that the supplier of the plunger rod of the PFS is (b) (4)
<b>Reviewer Comments:</b> Response is acceptable.

**Reviewer's Overall Assessment and Recommendations:** Product description information is sufficient.

## II. Manufacturing

### A. Manufacturers

From Module 3.2.P.3.1 [rMenB/OMV NZ], for the **commercial MenB liquid component**:

Facility	Responsibility
GlaxoSmithKline Vaccines S.r.l. (Rosia)	<ul style="list-style-type: none"> <li>- Formulation and filling</li> <li>- Visual inspection</li> <li>- Quality Control and Stability testing</li> <li>- Warehousing operations</li> </ul>
GlaxoSmithKline Vaccines S.r.l. Bellaria-Rosia 53018 Sovicille (SI) Italy	
(b) (4) GlaxoSmithKline Vaccines (b) (4)	
(b) (4) GlaxoSmithKline Vaccines (b) (4)	
(b) (4)	- Warehousing operations
(b) (4)	- Warehousing operations

**dba or d/b/a:** Doing business as;

**S.r.l.:** Società a responsabilità limitata (llc: limited liability company)

From Module 3.2.P.3.1 [MenABCWY], regarding **commercial final product (final pack) and MenABCWY RV**:

Facility	Responsibility
GlaxoSmithKline Vaccines S.r.l. (Rosia)  GlaxoSmithKline Vaccines S.r.l. Bellaria-Rosia 53018 Sovicille (SI) Italy	- Labelling and packaging operations of final product - Quality Control and Stability testing of MenABCWY RV and final product <sup>1</sup> - Quality Assurance release of final product - Warehousing operations
(b) (4) GlaxoSmithKline Vaccines (b) (4)	- Labelling and packaging operations of final product - Quality Control testing of final product <sup>1</sup> - Quality Assurance release of final product - Warehousing operations
(b) (4)	
(b) (4)	- Warehousing operations
(b) (4)	
(b) (4)	- Warehousing operations
(b) (4)	

**dba or d/b/a:** Doing business as;

**S.r.l.:** Società a responsabilità limitata (llc: limited liability company)

**RV:** Reconstituted Vaccine

<sup>1</sup> Quality Control testing at this site is limited to the post packaging Identity test performed to fulfil the requirement to distinguish the packaged product component from any other product being processed in the same packaging site, according to Title 21 of Code of Federal Regulations (CFR).

## B. Manufacturing Process

From 3.2.P.3.3 Description of Manufacturing Process and Process Controls Filling and Visual Inspection:

(b) (4)

Syringe Preparation: “Released syringes are received from the manufacturer [sterilized], (b) (4) and ready-to-use. Sterile syringe (b) (4) are (b) (4) room and placed on the (b) (4) of the (b) (4). They are (b) (4) [sterilized] by (b) (4) and are (b) (4) from the (b) (4) of the (b) (4) into the (b) (4)

Plunger Stopper Preparation: “Released stoppers (b) (4) are received from the manufacturer clean, (b) (4), [sterilized] and ready-to-use. For their use on the (b) (4), the stoppers are aseptically (b) (4)

Aseptic Filling: “When (b) (4) checks indicate that the filling process is delivering consistent (b) (4). The target fill volume includes an (b) (4)

. During the filling step, (b) (4) checks are automatically performed. The filling target (b) (4) can be adjusted to assure the delivery of vaccine’s nominal dose. It is measured at determined intervals throughout filling operations.”

Inspection and Storage: “Assembled containers are visually inspected for fill volume, particles and conformity of the container closure system. Non-conforming containers are rejected, accounted for and discarded. A defined number of containers are sampled from each batch for QC release testing according to QC Release Monographs. Inspected and approved containers are placed in boxes, [palletized] and stored at the warehouse (2-8 °C), awaiting labeling and packaging.”

Assembly and Labeling (from Module 3.2.P.3.3 [MenABCWY RV]): (b) (4), which is then labelled with a self-adhesive label, overprinted with lot number, expiry date and additional variable data (if

(b) (4) ). The labelled syringe is introduced into a carton with the vial, followed with a product information insert (leaflet) (if applicable). Lot number, expiry date and additional variable data (if applicable) are printed on each individual carton. Cartons are checked and placed in shipping boxes. Shipping boxes are identified, [palletized] and stored at +2 to +8 °C, awaiting release and expedition.”

#### **i. In Process Controls**

As indicated above, “during the filling step, (b) (4) checks are automatically performed. The filling (b) (4) can be adjusted to assure the delivery of [the] vaccine’s nominal dose. It is measured at determined intervals throughout filling operations.” According to Table 1 in Module 3.2.P.3.3 Description of Manufacturing Process and Process Controls Filling and Visual Inspection, the (b) (4) with action limits of (b) (4)

Additionally, Table 1 in Module 3.2.P.3.4 Control of Critical Steps In-process Quality Decision Tests – Specifications and Analytical Procedures includes the following in-process Quality Decision test:

<b>Manufacturing Step</b>	<b>Process Stage</b>	<b>Test</b>	<b>Acceptance Criteria</b>
Filling	Inspection	Container closure integrity by (b) (4) method	(b) (4)

**Reviewer Comment:** Review of container closure integrity (CCIT) and the test method validation is deferred to OCBQ.

#### **ii. Final Product Specifications and Test Methods**

Per Table 1 in Module 3.2.P.5.1 Specifications, the only device performance metric included in the release specifications for both MenB Liquid (b) (4) and MenABCWY RV is Extractable Volume, with an acceptance criterion of (b) (4) 0.5mL. Per Module 3.2.P.5.2 Extractable Volume, the test method is performed per (b) (4).

The assay and validity criteria are described in Module 3.2.P.5.2 Analytical Procedures Extractable Volume:

Assay Description: (b) (4)

Validity Criteria: “The test is satisfactory (conforms) if the contents of all (b) (4) are found to be of equal volume by visual examination and if the calculated volume for each (b) (4) is found to be not less than the declared volume. If the batch conforms (meets both criteria), the end result is reported as the mean extractable volume (in mLs). If one of the requirements listed above is not met, the test does not conform and the end result is reported as the lowest volume obtained in the check of the nominal volume.”

An assay qualification report is provided in Module 3.2.R (VA-0000230848 Extractable Volume\_4CMenB) and is summarized in 3.2.P.5.3 Validation of Analytical Procedures Volume. Sample qualification is sufficient as the method is (b) (4), and the application evaluated intermediate precision.

- Samples: MenB liquid PFS lots (b) (4)
    - Lot (b) (4)
  - Study Design: (b) (4)
  - Evaluation: (b) (4)
- . For the method to be satisfactory, the following acceptance criteria were applied:
- (b) (4)
  - The results must be within the product specification (b) (4) 0.5 mL). The acceptance criterion has been established considering the variability recorded for other products packaged in syringe bottles.

Intermediate precision acceptance criteria and results are summarized in Table 3 of 3.2.P.5.3 Validation of Analytical Procedures Volume, recreated below. The qualification met acceptance criteria.

Acceptance Criteria	Results
(b) (4)	(b) (4)
0.5 mL)	
The results must be within the product specification (b) (4) 0.5 mL).	All of the results met the product specification.

### **iii. Batch Analyses**

Module 3.2.P.2.3 Manufacturing Process Development Overview states “MenB Liquid DP manufacturing process has evolved during MenABCWY vaccine development, leveraging on the knowledge gained on the commercial Bexsero vaccine... the start of

development of MenABCWY vaccine coincided with Bexsero Phase 3 clinical development and progressed after licensure of Bexsero vaccine.”

(b) (4)

Table 1 in Module 3.2.P.5.4 Batch Analyses (b) (4) contains batch analysis data for **MenB Liquid GMP development batches** (b) (4) (4CMenB final container lots filled in the 1.25 mL Luer Lock syringe with (b) (4) rubber tip cap and (b) (4) plunger stopper). The only device relevant metric is **extractable volume** (acceptance criteria (b) (4) 0.5mL). **All batches** (b) (4) met the acceptance criteria (b) (4), respectively).

**Reviewer Comment:** It appears batches (b) (4) are the same lots as (b) (4) that are identified in Table 5 of the MenB Liquid comparability study described in Module 3.2.P.3.5 Process Validation and/or Evaluation – (b) (4) Filling. They are all described as “MenB Liquid GMP development batches.”

Table 1 in Module 3.2.P.5.4 Batch Analyses PPQ Lot contains batch analysis data for **PPQ Lot (b) (4)**, which met acceptance criteria (b) (4) 0.5mL) for **extractable volume** (b) (4) mL). Similarly, Table 1 in Module 3.2.P.5.4 Batch Analyses Post-PPQ Lot contains batch analysis data for **Post-PPQ Lot (b) (4)**, which met acceptance criteria (b) (4) 0.5mL) for **extractable volume** (b) (4)

Table 1 in Module 3.2.P.5.4 Batch Analyses (b) (4) contains QC release testing data for (b) (4) **CMenB PPQ lots (b) (4)**, which were filled in final container using the filling line (b) (4), in Building (b) (4), Rosia, Italy. The only device relevant metric is **extractable volume** (acceptance criteria (b) (4) 0.50 mL). **All batches (b) (4) met the acceptance criteria ((b) (4)**, respectively). These lots reflect testing done for post-Bexsero licensure registration of **filling line (b) (4)**, which will be used for commercial manufacture of the MenB Liquid component of MenABCWY vaccine and was also used for the formulation and filling of the MenB Liquid PPQ and post-PPQ lots.

According to Table 1 (MenABCWY RV Lots – General Information) in Module 3.2.P.5.4 Batch Analyses Overview [MenABCWY], the **MenB Liquid PFS PPQ (b) (4) and Post-PPQ (b) (4)** batches were also used with batches of the MenACWY vials for batch analysis of the overall MenABCWY product. **All batches** (see table below) **met the acceptance criteria** (b) (4) 0.5mL).

(b) (4)

### C. Process Validation

(b) (4)

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



Comparability of extractable volume was also assessed for the **MenABCWY RV lots listed in [Batch Analysis](#) above** (“test batches”) and **reference batches** (MenABCWY RV batches (b) (4) made with MenB Liquid batch (b) (4) made with MenB Liquid batch (b) (4)). “All results of MenABCWY RV test batches are **above the lower specification limit** (extractable volume (b) (4) 0.5 mL) and **in alignment with reference batch data**.” Notably, the extractable volume test executed for the MenABCWY RV reference batches was performed using the (b) (4) method, while for the MenABCWY RV test batches the extractable volume test was executed using the (b) (4) method.

Additionally, in Amendment 7 (Sequence 0008), GSK provided information on performance qualification for labeling and packaging at the (b) (4) site: “As per GSK’s request in the MenABCWY Type B, Pre-BLA Meeting, IND 14605, Amendment 245; CRMTS# 15416 and as per CBER concurrence in the Type B, MenABCWY Pre-BLA Meeting WRO dated 29 January 2024 (IND 14605, Amendment 245; CRMTS# 15416), Building (b) (4) in (b) (4) has been included in the MenABCWY BLA as a labelling and packaging facility of the final packed product although the relevant Performance Qualification (PQ) was not completed before the MenABCWY BLA submission date. The Company confirms that the **PQ for (b) (4) has been successfully completed** and, **following CBER’s recommendation to provide the completed PQ by mid-cycle of the BLA review cycle**, is submitting the relevant **PQ report within this quality information amendment** (please refer to the report PQ report (b) (4) Labelling Packaging line).”

The submitted report “documents the performance qualification for the (b) (4) syringe format with a (b) (4), and the (b) (4) is responsible for the primary container labeling of pre-filled syringes and the secondary and tertiary packaging operation of those syringes into cartons and shippers.”

PQ consisted of (b) (4) runs with a minimum batch size for this qualification is (b) (4) syringes (there is no maximum batch size quantity for packaging batches):

- (b) (4)

Samples were be (b) (4) The AQL sampling plan included examination of the following syringe defects (from Section 17.2 of “PQ report (b) (4) Labelling Packaging line” in Module 1.11.1 of Amendment 7 (Sequence 0008)):

**Syringe Defects:**

(b) (4)

No syringe defects were observed in any of the samples. The overall study met the process qualification acceptance criteria.

**Reviewer's Overall Assessment and Recommendations:** *Manufacturing information is sufficient.*

**III. Design Verification**

Section 1.6.2 of Module 3.2.P.2.4 Container Closure System provides a “high-level” summary of design input requirements:

- (b) (4)

Section 1.6.3 states “Design outputs for the 1.25 mL Luer Lock syringe with (b) (4) rubber tip cap and (b) (4) rubber stopper include:

- (b) (4)

Section 1.6.4 lists design verification activities performed by the suppliers:

- (b) (4)

- (b) (4)
- Plunger stopper (b) (4)  
(b) (4)
  - Plunger rod  
(b) (4)

This section also states, “Additional design verification activities were performed by GSK on the combination products.” Tables 16-18 in Module 3.2.P.2.4 describe QC testing individual component per the tabulated specifications and acceptance criteria described in Module 3.2.P.7 (captured in [Appendix 1](#) of this memo). They tested (b) (4) batches of syringe barrels from each supplier (b) (4) batches of (b) (4) plunger stoppers and (iii) (b) (4) batches of plunger rods. The batch numbers as well as executed tests and acceptance criteria are tabulated below. All batches met acceptance criteria.

(b) (4)

**Reviewer Comment:** *It's not clear whether the statement "additional design verification activities were performed by GSK on the combination products" refers to the QC testing described above or some other testing.*

Section 1.6.2 in Module 3.2.P.2.4 provides a high-level summary of design input requirements, including that "The prefilled syringe must meet functionality requirements from ISO (b) (4)

**Reviewer Comment:** *Notably, ISO (b) (4) is not formally recognized by FDA. However, the standard can provide a framework that can be helpful for sponsors/applicants to provide and organize information regarding PFS syringe verification. Unfortunately, GSK did not go into detail about how the final combination product meets the requirements of ISO (b) (4). Additionally, GSK did not identify the essential performance requirements (EPRs) for their combination product. Typical EPRs for product that include a PFS used for reconstitution and injection are deliverable volume, (b) (4). Cap removal force is also sometimes included as an EPR. GSK provided adequate information to demonstrate verification of deliverable volume (extractable volume of the MenB Liquid PFS and the MenABCWY RV), but there is no information regarding (b) (4) for the product. It's acknowledged that (b) (4) were verified for Bexsero (see device memo for BLA 125546/963) and GSK is leveraging much information from the Bexsero product development. However, although the MenB Liquid PFS and Bexsero have the same formulation and utilize the same PFS components, there are differences in proposed clinical use. Bexsero is filled with the final formulation of the vaccine (i.e., no reconstitution steps), whereas the MenABCWY combination product involves multiple steps (reconstitution, withdrawal from vial, injection). Verification of EPRs that is representative of the proposed clinical use, or a scientific rationale for an alternative approach, is needed. See **IR#18.1** below.*

**Information Request (IR)#18.1**

**Date Sent:** August 13, 2024

**Date/Amd/eCTD Sequence Received:** August 27, 2024/23/0025

**IR Comment:** You did not identify your essential performance requirements (EPRs) for the MenABCWY combination product. EPRs for PFS typically include deliverable volume (volume of injection), (b) (4) (force required to withdraw reconstituted vaccine from the drug product vial). You provided data to verify the volume of injection. However, you have not provided adequate information to demonstrate verification of (b) (4) for the MenABCWY combination product. The (b) (4) verification data in Tables 16 and 17 of Module 3.2.P.2.4 Container Closure System [MenB Liquid] and Tables 17 in Module 2.3.1 is not reflective of the proposed clinical use, as it appears the testing is conducted with (b) (4) syringes and not with the final combination product (MenACWY vial, MenB Liquid PFS, and necessary needles). You also state that "additional design verification activities were performed by GSK on the combination products," but it is not clear what information this is referring to. Verification data is necessary to demonstrate that the MenABCWY combination

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product meets its EPRs representative of the proposed clinical use. We acknowledge that Module 3.2.P.2.4 Container Closure System [MenB Liquid] states that “data generated using Bexsero vaccine is considered fully applicable to MenB Liquid component due to the equivalence of the PFS and the product composition, as the only difference is in the (b) (4) of MenB Liquid compared to Bexsero.” Although the MenB Liquid PFS and Bexsero have the same formulation and utilize the same PFS components, there are differences in proposed clinical use. Bexsero is filled with the final formulation of the vaccine (i.e., no reconstitution steps), whereas the MenABCWY combination product involves multiple steps (reconstitution, withdrawal from vial, injection). Please provide verification data for (b) (4) that is representative of the clinical use (i.e., reconstitution, withdrawal from vial, injection) using the components of the MenABCWY combination product and necessary needles. Alternatively, please provide a justification for why your current information and previous verification data conducted for the Bexsero PFS is sufficient to conclude that the MenABCWY combination product meets (b) (4) requirements. In the latter approach, please submit a tabulated summary of the leveraged Bexsero PFS verification data (specifications, acceptance criteria, test methods, and results) for completeness.

**Applicant Response:** “The Company would like to indicate that the requested verification data for (b) (4) that is representative of the clinical use (i.e., reconstitution, withdrawal from vial, injection) using the components of the MenABCWY combination product and necessary needles are **not currently available. However, the Company believes, based on current data and evidence available, that the functionality of the pre-filled syringe (PFS) with MenABCWY vaccine is demonstrated** based on:”

- Systematic **control strategy** established for incoming material release
- **Practical test** data generated with Bexsero and MenB Liquid drug products and available Bexsero design verification data
- Use Related Risk Analysis (**URRA**)

“The Company is confident that (b) (4) device is functioning properly and meets required performance metrics when used with MenABCWY vaccine. **As a matter of verification, the Company is proposing to perform EPR testing**, specifically evaluation of (b) (4) (also referred to as (b) (4) and (b) (4), with the MenABCWY combination product as described in section 4.”

*(Information below is summarized from applicant response)*

**Incoming Material Testing:**


- (b) (4)

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○ (b) (4)



Bexsero and MenB Liquid Component Data:

**Information Request (IR)#18.1****Date Sent:** August 13, 2024**Date/Amd/eCTD Sequence Received:** August 27, 2024/23/0025**Table 1 Overview of Bexsero data supporting EPRs for MenABCWY combination product**

Step	Test	Supportive data
<b>Reconstitution step</b> (slowly dispense entire content of syringe into the vial). This step corresponds to the first- time usage of the PFS filled with MenB Liquid drug product and therefore to the first movement of the plunger of the syringe.	(b) (4)	Considering that Bexsero and MenB Liquid drug products are identical in terms of formulation/composition and PFS components used, EPRs of reconstitution step are considered to be fully covered by available Bexsero design verification data and practical test data generated with Bexsero and MenB Liquid: <ul style="list-style-type: none"><li>- Practical test data (see 2.1)</li><li>- Design verification data (see 2.2)</li></ul>
<b>Withdrawal step</b> (withdrawal of entire content of reconstituted product from the vial back into the same PFS)		(b) (4)
<b>Administration step</b> (administer reconstituted product intramuscularly)		(b) (4)

RV: Reconstituted Vaccine; EPR: Essential Performance Requirements; PFS: Pre-Filled Syringe (also referred to as (b) (4))

(b) (4)

**Practical Test:**

- actions **representative of clinical use of MenABCWY reconstitution step** are applied as part of the practical test performed during the long-term and accelerated stability follow up of the (b) (4) Bexsero lots ((b) (4))

**Information Request (IR)#18.1****Date Sent:** August 13, 2024**Date/Amd/eCTD Sequence Received:** August 27, 2024/23/0025**Table 2** Summary of practical test results available for MenB Liquid drug product filled in (b) (4)

Stability study	Time Point	Practical test result <sup>1</sup>
Long-term real-time conditions (at 2°C to +8°C)	0 months	Conform
	36 months	Conform
	48 months	NA
Accelerated condition (at (b) (4))	(b) (4)	
(b) (4)		

NA: Not Available yet

1. Acceptance criteria: (b) (4)

**Bexsero Design Verification Data:**

- (b) (4)

- (b) (4)



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- (b) (4) at subsequent withdrawal and administration steps are expected to meet the required acceptance criteria:
  - (b) (4)

**URRA:**

- “21 October 2021 IND 14605 amendment consisting of a Human Factor (HF) Bridging Submission (GSK SN: 0612) including userelated risk analysis (URRA) based on post-marketing data from (b) (4) marketed outside the US (as it applies to MenABCWY as agreed with CBER on 22 April 2021), and a threshold analysis to compare the physical presentation, user tasks, and labelling information between the two products and thus comprehensively and systematically evaluate all tasks involved in the use of the MenABCWY vaccine, including errors that users might commit or the tasks they might fail to perform, and the potential negative clinical consequences of use errors and tasks failures.”
- “The Company has therefore determined from the risk analysis, existing (b) (4) post-marketing safety data are sufficient to support also MenABCWY HCP administration of the product. On 21 December 2021, CBER agreed that based on the data package provided by the Company, no human factors validation study for MenABCWY was needed.”

**Data Generation Plan:**

**Information Request (IR)#18.1****Date Sent:** August 13, 2024**Date/Amd/eCTD Sequence Received:** August 27, 2024/23/0025

(b) (4)

(b) (4) months results are planned to be **available in January 2025**. The Company commits to provide them as **post-approval commitment** after the BLA approval.

**Reviewer Comments:** *This product is lower risk from a device perspective, and GSK's rationale for the adequacy of current Bexerso and MenB Liquid is acceptable. Furthermore, this rationale was accepted for implementation of the (b) (4) (BLA 125347/501) (b) (4), which has the same clinical use steps (i.e., reconstitution, withdrawal, injection). GSK's proposal to conduct explicit verification testing is acceptable. An IR will be sent to acknowledge the proposal, indicating that the data should be submitted as a product correspondences as it becomes available.*

**Follow-on IR#33.4****Date Sent:** November 26, 2024**Date/Amd/eCTD Sequence Received:** December 4, 2024/48/0050

**IR Comment:** In your August 27, 2024, response to Comment in of Information Request #18 dated August 13, 2024, you stated "the requested verification data for (b) (4) that is representative of the clinical use (i.e., reconstitution, withdrawal from vial, injection) using the components of the MenABCWY combination product and necessary needles are not currently available." In addition to your rationale that the current data and available evidence demonstrate the functionality of the PFS, you also propose to perform EPR testing, specifically evaluation of (b) (4)

<p><b>Follow-on IR#33.4</b></p> <p><b>Date Sent:</b> November 26, 2024</p> <p><b>Date/Amd/eCTD Sequence Received:</b> December 4, 2024/48/0050</p>
<p>(also referred to as (b) (4) ) and (b) (4) , with the MenABCWY combination product. The proposed study described in Table 4 of your response appears reasonable and we acknowledge your commitment to provide the (b) (4) months results post-approval. Please address the following:</p> <p>a. Please confirm you are also committing to provide the T48 month data when it becomes available.</p> <p>b. Please provide this information in product correspondences as the data becomes available.</p>
<p><b>Applicant Response:</b> The Company acknowledges CBERs' request and commit to provide Essential Performance Requirements (EPR) testing data using the components of the MenABCWY combination product at T48 months, in addition to (b) (4) month data. As recommended by CBER, the Company commits to submit (b) (4) month and T48 month data as it becomes available through Product Correspondences to MenABCWY BLA.</p>
<p><b>Reviewer Comments:</b> Response is acceptable.</p>

**Reviewer's Overall Assessment and Recommendations:** Design verification information in the submission and provided in response to IR#18, are sufficient for approval, considering the lower risk profile of this device constituent and GSK's commitment to conduct additional verification and stability testing.

#### IV. Design Validation

Refer to review Human Factors consult review memo from Avani Bhalodia, CDER/OSE/OMEPRM/DMEPA1. During the review period, the consult reviewer reached out to the CBER review with questions related to the review. CBER device reviewer provided responses as indicated below:

##### Question:

1.Are there any other similar products available using a non-graduated syringe in a similar manner?

##### Response:

HIBERIX (BLA 125347)  
PENBRAYA (BLA 125770)  
IXCHIQ BLA (125777)

##### Question:

2.Based on our review of the use-related risk assessment rationale and the proposed change to the PFS design, we maintain our determination that the Applicant does not need to submit human factors validation study results with this marketing application. I just wanted to confirm that CBER does not have any concern with the proposed non-graduated syringe?

Response: No concerns

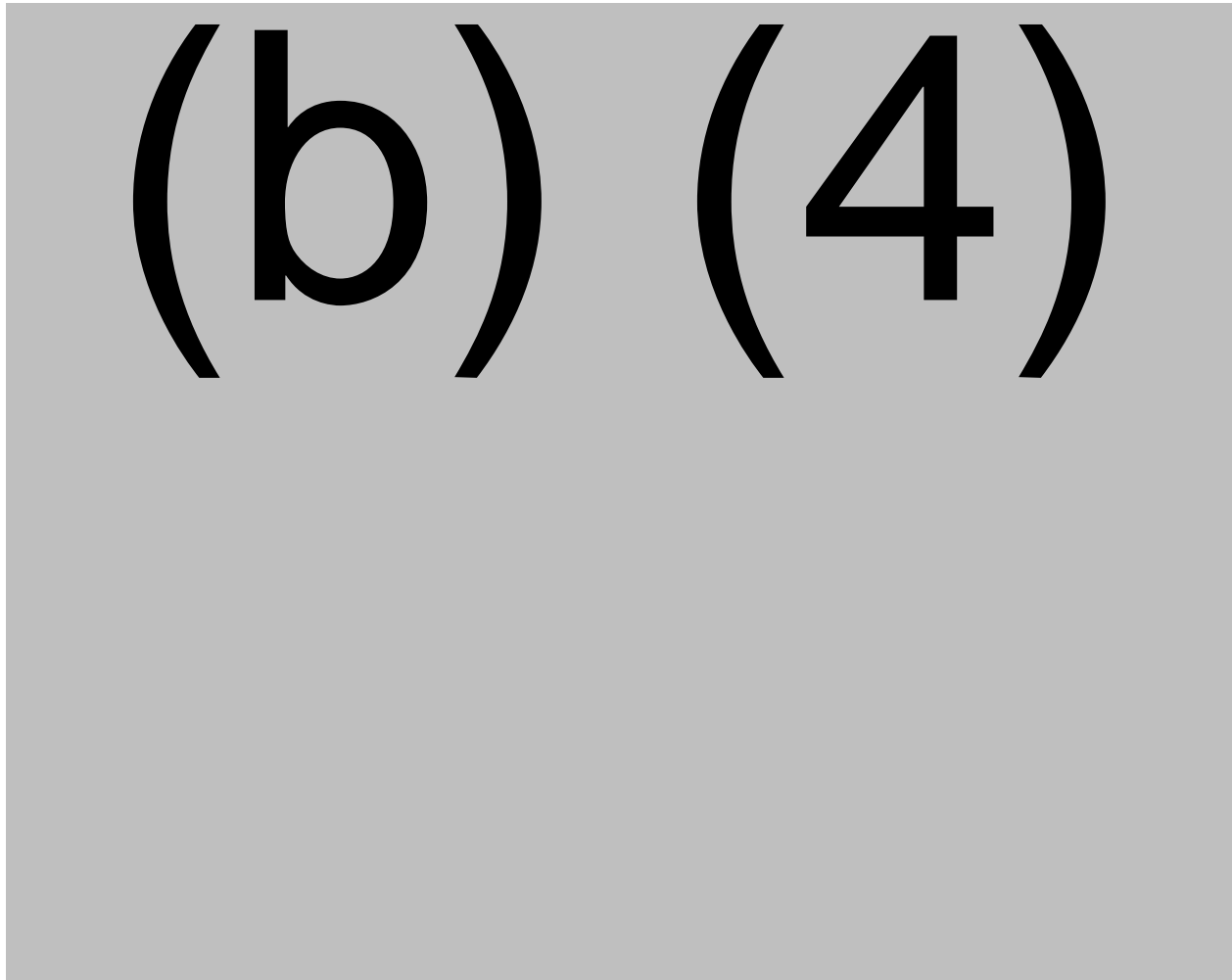
**Reviewer's Overall Assessment and Recommendations:** No concerns from device perspective. Defer to the HF reviewer assessment.

## **V. Biocompatibility**

Biocompatibility information was provided in Section 1.3.2 of Module 3.2.P.2.4 Container Closure System.

Contact Classification (identified by GSK):

- rubber tip cap, plunger stopper and syringe barrel:
- syringe barrel, the Luer Lock adapter, the rigid cap, and the plunger rod: surface device with intact skin contact and limited contact duration (b) (4)



**Reviewer Comment:** The syringe components are the same as those in the rest of GSK's vaccine portfolio, due to their (b) (4) harmonization effort. The biocompatibility of the syringe components was previously assessed in the corresponding supplements for the BLAs for those vaccines, including Bexsero (BLA 125546/963 (Sequence 0583)). In those BLA supplements previously submitted as part of their (b) (4) syringe harmonization effort, the biocompatibility information referenced to (b) (4) for

the syringe barrel assembly (including rubber tip cap) was deemed sufficient. A rationale for applicability of (b) (4) biocompatibility results to the (b) (4) syringe barrels was also provided and was determined to be acceptable. In those supplements, plunger stopper biocompatibility was leveraged from its previous use in GSK's other vaccine PFS products prior the (b) (4) harmonization effort. There are no new biocompatibility concerns for the use of the syringe in the current BLA. New DMF memos will not be generated.

**Reviewer's Overall Assessment and Recommendations:** Biocompatibility information is acceptable. Assessment of extractables and leachables information deferred to CMC.

## VI. Sterilization

Module 3.2.P.2.4 Container Closure states the syringe barrels and plunger stoppers are received cleaned, siliconized, and sterile. The **plunger stoppers** are sterilized via (b) (4), in accordance with ISO standard (b) (4).

The **syringe barrels** are sterilized via (b) (4) in accordance with ISO standard (b) (4). GSK provides results of (b) (4) syringe barrel lots from (b) (4), stating the results comply with limits stated in ISO (b) (4).

(b) (4)

(b) (4)

**Reviewer Comment:** Regarding the acceptance criteria, the sterilant residual limits in ISO (b) (4) are expressed in units of expressed as maximum average daily doses (e.g., mg/day). For a limited exposure device (cumulative sum of single, multiple, or repeated contact is up to (b) (4)), the average (b) (4) dose of (b) (4) should

not exceed (b) (4) (respectively). The worst-case limit of (b) (4) residuals are (b) (4) per vaccine (b) (4), respectively, which are orders of magnitude below the limits specified in ISO (b) (4). Therefore, GSK's acceptance criterion for sterilant residuals and the suppliers' acceptance criteria for (b) (4) are acceptable.

Section 1.4.4 in Module 3.2.P.2.4 states "QC release specifications of the empty syringe barrel with tip closure system and of the (b) (4) plunger stopper include sterility tests (sterility test (b) (4) and sterility test (b) (4) according to (b) (4) Sterility Tests)."

**Reviewer's Overall Assessment and Recommendations:** Sterilization information is sufficient from a device perspective. Sterility and endotoxin levels of the PFS contents are deferred to CMC review. Sterilization validation and container closure integrity are deferred to OCBQ/DMPQ.

## VII. Control Strategy

Essential Performance Requirement	Control Strategy Description (e.g., incoming acceptance, in-process control, release testing activities):
(b) (4)	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)

**Reviewer's Overall Assessment and Recommendations:** Control strategy is adequate for the lower risk profile of this device constituent.

## VIII. Packaging, Stability, Shipping

### A. Packaging

Module 3.2.P.3.3 [MenABCWY RV] explains that after labeling, vials and syringes are introduced into cartons (together) along with "a product information insert (leaflet) (if applicable). Lot number, expiry date and additional variable data (if applicable) are printed on each individual carton. Cartons are checked and placed in shipping boxes. Shipping boxes are identified, palletised and stored at +2 to +8 °C, awaiting release and expedition."

Amendment 7 (Sequence 0008) indicates that “Packaging Line (b) (4) in Building (b) (4) Site is a syringe and vial packaging line for secondary and tertiary packaging operations. The line is currently qualified to run the following formats:

- (b) (4)

In response (December 5, 2024, amendment 49, sequence 0051) to CMC IR#35 sent November 29, 2024, GSK provided an image of the final packaging configuration (below) with the following explanation: “The PENMENVY carton is a single layer with contents as follows: 10-single-dose vials of lyophilized MenACWY component held by a folded partition on one side of the carton and 10 single-dose prefilled syringes (PFS) of liquid MenB component held by a folded partition on the other side of the same carton (positioned upside down, alternately).”

Figure 1 Image of PENMENVY components stored in the carton



The components on the image (carton, labels, and containers) are related to a test material not for human use.

## B. Stability

**Reviewer Comment:** The review below reflects updated stability data provided in Amendment 44 (Sequence 0046).

Proposed Shelf Life and Storage Conditions:

- MenB Liquid PFS: 48 months at +2°C - +8°C

Module 3.2.P.8.1 states “Stability data of **Bexsero commercial vaccine lots** considered relevant for MenB Liquid analytical and manufacturing process development have been provided.”

**Bexsero Data:**

- (b) (4)

The “**practical test**” involves the following, per Module 3.2.P.8.3:

(b) (4)

**On-going protocols for MenB Liquid PFS:**

MenB Lot	Use	Date of Manufacture	Batch Size (PFS)	Type of Study	Data Currently Available	Data
(b) (4)	Phase 3 clinical trials (Men-019, V72_72)	(b) (4)	(b) (4)	Long Term stability at +2°C - +8°C	48 months	3.2.P.8.3 Stability Data Long-Term - Phase 3 Clinical Lot  CCIT 6, 12, 24, 36, and 48 months  Practical test at release (0 months)
(b) (4)	PPQ to support the filling process of	(b) (4)	(b) (4)	Long Term stability	24 months	3.2.P.8.3 Stability Data Long-Term - PPQ Lot



	MenB liquid filled in (b) (4) line with a (b) (4) and using (b) (4) as primary container			at +2°C - +8°C		CCIT at release (0 months), 12, and 24 months
(b) (4)	Post-PPQ lot produced with drug substances including manufacturing changes as part of lifecycle management of Bexsero and reflected in the future MenABCWY commercial production. Lot was tested according to the commercial QC release specifications.	(b) (4)	(b) (4)	Long Term stability at +2°C - +8°C	18 months	3.2.P.8.3 Stability Data Long-Term Post-PPQ Lot  CCIT at release (0 months) and 12 months

#### Post-Approval Stability Protocol and Stability Commitments

- 3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment – Phase 3 Clinical Lot
  - MenB Liquid Phase 3 clinical trial lot (b) (4)
  - 48 Months at +2°C - +8°C
  - CCIT planned for 0, 6, 12, 24, 36, and 48 months
- 3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment – PPQ Lot
  - MenB Liquid PFS PPQ lot (b) (4)
  - (b) (4) Months at +2°C - +8°C
  - CCIT planned for 0, 12, 24, 36, 48, (b) (4) months
- 3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment – Post-PPQ Lot
  - MenB Liquid Phase 3 clinical trial lot (b) (4)
  - (b) (4) Months at +2°C - +8°C
  - CCIT planned for 0, 12, 24, 36, 48, (b) (4) months
- 3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment – Stability Monitoring of Commercial Lots
  - MenB Liquid PFS
  - (b) (4) Months at +2°C - +8°C
  - CCIT planned for 0, 12, 24, 36, 48, (b) (4) months
- 3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment – (b) (4)
  - (b) (4) MenB lots (b) (4)
  - (b) (4) months at +2°C - +8°C

- CCIT planned for 0, 12, 24, 36, 48, (b) (4) months
- Practical test planned for 0, 36, 48, (b) (4) months

Stability data for the reconstituted vaccine (Module 3.2.P.8 [MenABCWY]) did not evaluate any device-relevant metrics.

**Reviewer Comment:** *The data referenced above appears to be inconsistent on inclusion of device-relevant metrics (i.e., CCIT as a surrogate for dose accuracy, practical test as a measure of functionality) or does not include them at all (i.e., (b) (4) ). EPRs may be stability indicating because these factors can be impacted by external stressors, including aging and environmental conditions. Thus, data verifying EPRs at expiry, or scientific rationale for its exclusion, is needed. See IR#18.2 below.*

#### Information Request (IR)#18.2

**Date Sent:** August 13, 2024

**Date/Amd/eCTD Sequence Received:** August 27, 2024/23/0025

**IR Comment:** Your long-term stability data includes a practical test. Additionally, you assessed syringe functionality after simulated shipping. These tests appear qualitative and primarily look for leakage and component integrity. Qualitative assessment of syringe function may not adequately verify that the syringe maintains EPRs (dose accuracy/extractable volume, (b) (4) ) at expiry. EPRs may be stability indicating because these factors can be impacted by external stressors, including aging and environmental conditions. Please provide data demonstrating (b) (4) continue to meet acceptance criteria at expiry. Please also include specifications and acceptance criteria for these injection forces in the long-term stability program. Alternatively, please provide a justification for why your current information and stability plan, or any previous stability data leveraged from the Bexsero PFS, are sufficient to conclude that the MenABCWY combination product meets (b) (4) requirements at expiry and after shipping. In the latter approach, please submit a tabulated summary of any leveraged Bexsero PFS stability data (specifications, acceptance criteria, test methods, and results) for completeness.

**Applicant Response:** The Company acknowledges that MenABCWY data demonstrating (b) (4) continue to meet acceptance criteria at expiry is not currently available.

As described in response to Question 1, as a matter of confirmation/verification, the evaluation of EPRs at expiry has been included in the long-term stability protocol currently ongoing on Bexsero final container lots supporting the implementation of (b) (4) device system. The testing is also planned to be performed in the study launched for MenABCWY (please refer to Table 4).

However, the Company is confident in the functionality of the (b) (4) syringe over product shelf-life based on following data:

**Information Request (IR)#18.2****Date Sent:** August 13, 2024**Date/Amd/eCTD Sequence Received:** August 27, 2024/23/0025

- Verification data generated at expiry for different GSKs' combination products filled in previously used syringe type and the similarity between that syringe type and (b) (4) , which is proposed for MenABCWY.
- Extensive knowledge from post-marketing surveillance data around the previous syringe system that is similar to (b) (4) .
- The control strategy in place for the incoming material at release.
- Practical test, design verification data and scientific rational supporting the Company's position that (b) (4)   
 (b) (4) step support the actions required at withdrawal and injection steps as presented in response to Question 1.

Verification data generated at expiry of different combination products filled in previously used PFS system

Stability information from the previously used syringes demonstrating essential performance requirements (specifically extractable volume or container closure (b) (4) are maintained at expiry are available for different GSK combination products as summarized in Table 5.

This data is deemed supportive of (b) (4) device performance metrics at expiry of MenABCWY vaccine considering the similarity between (b) (4) and previous PFS devices (please also refer to MenB Liquid section 3.2.P.2.3 Manufacturing Process Development – MenB Liquid Specific Development – (b) (4)

(b) (4) , Table 1, page 5):

- (b) (4)

(b) (4)

(see [Section VIII.C Shipping](#) in this memo for the remainder of the applicant response)

**Reviewer Comments:** *This product is lower risk from a device perspective, and GSK's rationale for the adequacy of current Bexerso and MenB Liquid information is acceptable. The data from current approved GSK vaccines that use the same syringe components is also encouraging. GSK's proposal to conduct explicit verification of EPRs after long term storage (48 months) is acceptable. See IR#33.4 in [Section III. Design Verification](#) in this memo.*

### C. Shipping

(b) (4)



- (b) (4)

**Reviewer Comment:** The shipping simulation method appears acceptable. The functionality testing appears to be qualitative. Qualitative assessment of syringe function may not adequately verify that the syringe maintains EPRs (dose accuracy/extractable volume, (b) (4) Data verifying EPRs at after shipping, or scientific rationale for its exclusion, is needed. See **IR#18.2** below.

#### **Information Request (IR)#18.2**

**Date Sent:** August 13, 2024

**Date/Amd/eCTD Sequence Received:** August 27, 2024/23/0025

**IR Comment:** Your long-term stability data includes a practical test. Additionally, you assessed syringe functionality after simulated shipping. These tests appear qualitative and primarily look for leakage and component integrity. Qualitative assessment of syringe function may not adequately verify that the syringe maintains EPRs (dose accuracy/extractable volume, (b) (4) at expiry. EPRs may be stability indicating because these factors can be impacted by external stressors, including aging and environmental conditions. Please provide data demonstrating (b) (4) continue to meet acceptance criteria at expiry. Please also include specifications and acceptance criteria for these injection forces in the long-term stability program. Alternatively, please provide a justification for why your current information and stability plan, or any previous stability data leveraged from the Bexsero PFS, are sufficient to conclude that the MenABCWY combination product meets (b) (4) requirements at expiry and after shipping. In the latter approach, please submit a tabulated summary of any leveraged Bexsero PFS stability data (specifications, acceptance criteria, test methods, and results) for completeness.

**Applicant Response:** (see [Section VIII.B Stability](#) in this memo for the beginning part of the applicant response)

With regards to potential impact of shipping on the device functionality, the Company would like to refer to section 3.2.P.2.3 Manufacturing Process Development – MenB Liquid Specific Development – (b) (4), where shipping simulation data is provided (see section 1.4.2.2, page 21).

The purpose of the shipping simulation study was to qualify the physical integrity of (b) (4) during its shipping by demonstrating that the syringe container closure integrity is not impacted by a sequence of tests simulating the shipping environment physical hazards during international shipments (including air, road, and sea travel simulation).

In addition, a syringe functionality test (practical test) was performed after shipping simulation to confirm that the shipping does not impact their functionality. The description of the practical test performed on (b) (4) as part of simulated shipping is provided here below:

**Information Request (IR)#18.2****Date Sent:** August 13, 2024**Date/Amd/eCTD Sequence Received:** August 27, 2024/23/0025

- Method description: The aim of the test is to demonstrate the syringe functionality by checking that the syringe is suitable for use and operates properly, without blocking and leakage. The test is to be performed on (b) (4) syringes. The test procedure as detailed in the Company's SOP 9000001609 is provided hereafter:
  - (b) (4)
- Acceptance criteria: The test is PASS if the syringes operate properly, without blocking and leakage.
- Results: All results passed the acceptance criteria (i.e., the syringes operate properly, without blocking and leakage).

The Company acknowledges that the practical testing conducted as part of the shipping validation is not a direct simulation of the clinical use (i.e., reconstitution, withdrawal from vial, injection). However, the functional test does demonstrate the syringe functionality by checking that the syringe operates properly without blocking and leakage.

As mentioned in response to Question 1 (see paragraph 2.2), the (b) (4) is fully representative of the clinical process. Indeed, the HCP does it only (b) (4). Furthermore, the initial movement of the plunger to dispense the liquid into a vial is expected to be the most critical during the reconstitution step when the liquid is transferred from PFS into the vial and the (b) (4) are expected to be higher compared to subsequent (b) (4) (i.e., the first movement of the syringe plunger stopper which remained immobile over the shelf-life of the product compared to subsequent manipulations by the HCP). The administration needles (b) (4) was used for all tests, which represents the worst case as justified in 2.2).

Furthermore, as discussed in the response to Question 1, the URRA data demonstrate the PFS and vial combination, administration instructions, and labeling can be used safely and effectively by the intended user population (HCPs).

In conclusion, the practical testing adequately demonstrates that EPRs are maintained after shipping.

**Reviewer Comments:** *GSKs arguments for the adequacy of the functionality test after shipping are reasonable.*

Notably, in response (December 9, 2024, Amendment 51, Sequence 0053) to CMC IR#34 sent November 27, 2024, GSK agreed to shorten the shelf-life of the

MenACWY Lyo component to 18 months at +2 to +8°C. GSK states “Once additional stability data are available confirming that the commercial process consistently delivers MenACWY Lyo lots with stability profiles supporting (b) (4), we will proceed with (b) (4).”

**Reviewer’s Overall Assessment and Recommendations:** *Packaging, stability, and shipping information providing in the submission and via IR#18 is adequate.*

## IX. Comparability Protocols

None submitted.

## X. Quality System

Section 1.6 states “In order to comply with the current good manufacturing practices for combination products, the Company has applied the streamlined approach in accordance with 21 CFR part 4.4(b)(1), which consists in demonstrating compliance with the full drug/biologic cGMP regulation plus the applicable specified provisions from the medical device quality system (QS) regulation (i.e. 21 CFR 820.20 Management responsibility, 820.30 Design controls, 820.50 Purchasing controls and 820.100 Corrective and preventive actions).”

Device GMP Requirement	Responsible Firm(s):	Summary
21 CFR 820.20 Management Responsibility	GlaxoSmithKline Vaccines S.r.l., Rosia site, Italy  (b) (4)  GlaxoSmithKline Vaccines, (b) (4) site, United States	<i>Deferred to OCBQ/DMPQ review. See CMC/DMPQ IR#3 below.</i>
21 CFR 820.30 Design Controls	GlaxoSmithKline Vaccines S.r.l., Rosia site, Italy  (b) (4)  GlaxoSmithKline Vaccines, (b) (4) site, United States	Section 1.6 of 3.2.P.2.4 Container Closure System states “In accordance with 21 CFR 820.30, a design history file was prepared for the 1.25 mL Luer Lock syringe with (b) (4) rubber tip cap and (b) (4) rubber stopper.”  The section then summarizes how GSK activities related to device development, design inputs, design outputs, design verification.



Device GMP Requirement	Responsible Firm(s):	Summary
21 CFR 820.50 Purchasing Controls	<p>GlaxoSmithKline Vaccines S.r.l., Rosia site, Italy</p> <p>(b) (4)</p> <p>GlaxoSmithKline Vaccines, (b) (4) site, United States</p>	<p>From Section 1.7 of 3.2.P.2.4 Container Closure System:</p> <p>"Information related to purchasing controls of the 1.25 mL Luer Lock syringe with (b) (4) rubber tip cap and (b) (4) rubber stopper is provided hereafter:</p> <ul style="list-style-type: none"> <li>• (b) (4) were selected and are managed based on specific Company's procedures for suppliers' selection, approval, and control.</li> <li>• The Company has a quality agreement in place with both (b) (4).</li> <li>• The Company has a supply agreement in place with both (b) (4).</li> <li>• Both (b) (4) are audited at defined frequency according to the Company's procedures.</li> <li>• Requirements related to change notifications are defined in the quality agreements. The Company is informed in advance of supplier's changes that may have the potential to impact device design and validation status. The management of vendor changes is performed according to the Company's procedure."</li> </ul> <p><i>See also CMC/DMPQ IR#3 below.</i></p>
21 CFR 820.100 Corrective and Preventive Actions	<p>GlaxoSmithKline Vaccines S.r.l., Rosia site, Italy</p> <p>(b) (4)</p> <p>GlaxoSmithKline Vaccines, (b) (4) site, United States</p>	<p><i>Deferred to OCBQ/DMPQ review. See CMC/DMPQ IR#3 below.</i></p>
21 CFR 820.170 Installation	N/A	N/A

Device GMP Requirement	Responsible Firm(s):	Summary
21 CFR 820.200 Servicing	N/A	N/A

**Information Request (IR)#3.5 (CMC/DMPQ)**

**Date Sent:** April 22, 2024

**Date/Amd/eCTD Sequence Received:** May 3, 2024/#/0005; May 22, 2024//0008

**IR Comment:** In Section 3.2.P.2.4 Pharmaceutical Development – Container Closure System, you state compliance with 21 CFR 820.20 Management responsibility, 820.50 Purchasing controls and 820.100 Corrective and preventive actions (CAPA). However, according to “Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff (2003)”, applicants should provide a copy of basic Quality System (QS) procedures (21 CFR 820.20e), procedures for purchasing controls (21 CFR 820.50), and CAPA procedures (21 CFR 820.100). It appears that procedures regarding your QS and CAPA systems was not provided. Regarding device purchasing controls, only a brief summary was provided. Since it is necessary to evaluate your compliance with the medical device QS regulations, please provide the following:

- a. A copy of your basic QS procedures, including quality or internal audit procedures, management review procedures, and an outline of the structure of the quality system documentation.
- b. A copy of your procedures for purchasing controls, including your supplier evaluation process, supplier records management, and a description of how you balance purchasing assessments and receiving acceptance.
- c. A copy of your CAPA system procedures, including a description of how your CAPA system is tied to your management program, an explanation of how your CAPA system addresses nonconforming practices as well as nonconforming product, a summary of your CAPA effectiveness procedure, CAPA information subject to management review, and an explanation of how the CAPA system interacts with your design change control and risk management systems.

**Applicant Response:**

**Amd 4/Sequence 0005**

To address and meet the requirements of the Current Good Manufacturing Practice (CGMP) for MenB Liquid combination product provided in pre-filled syringe, in line with 21 CFR 4.4(b)(1), the Company has implemented a CGMP operating system based on the "drug CGMP-based" streamlined approach.

The same quality system is already implemented for approved Bexsero combination product that is supplied in the same pre-filled syringe and manufactured in the same facilities as MenB Liquid component. The Company confirms that the requested quality system procedures have been established at the involved facilities. Since some of them need to be translated, they will be all provided by the end of May 2024.

**Information Request (IR)#3.5 (CMC/DMPQ)****Date Sent:** April 22, 2024**Date/Amd/eCTD Sequence Received:** May 3, 2024/#/0005; May 22, 2024//0008**Amd 7/Sequence 0008 (summary)**

This amendment contains additional information on the QMS procedures at GlaxoSmithKline Vaccines S.r.l., Rosia site, Italy and (b) (4) GlaxoSmithKline Vaccines, (b) (4) site, United States. Table 1 in this information describes and links to supporting documents for basic QS procured, purchasing controls, and CAPA. Notably, the purchasing controls information states "Procedures for purchasing controls are part of the GSK quality management system. Suppliers, service providers, and consultants must be assessed and evaluated for their ability to meet quality requirements and other specified criteria. Each material is purchased against a specification that defines the attributes that affect material quality and usability, and quality agreements are implemented between GSK and suppliers and service providers.

Testing is performed on receipt of materials until supplier reliability has been established. Upon confirmation of acceptable quality, a reduced testing regime may be implemented, and materials may be accepted on the supplier's Certificate of Analysis/Conformity. Any changes which the supplier wishes to make are subject to a change control system between the supplier and GlaxoSmithKline."

**Reviewer Comments:** *IR and response included for informational purposes. Assessment of the information is deferred to DMPQ.*

***Reviewer's Overall Assessment and Recommendations:*** *QMS information provided in the application and in response IR#3 is sufficient for premarket review purposes from a device product office perspective (i.e., regarding design controls and purchasing controls). Assessment of management responsibility and CAPA is deferred to DMPQ.*

