

**CBER CMC BLA Review Memorandum**

**BLA STN 125819**

**PENMENVY**

**Meningococcal Groups A, B, C, W, and Y Vaccine**

**Marcos D. Battistel, Ph.D., Biologist/LABORATORY OF BACTERIAL  
POLYSACCHARIDES/DIVISION OF BACTERIAL PARASITIC AND ALLERGENIC  
PRODUCTS/OFFICE OF VACCINES RESEARCH AND REVIEW**

**Maria Florencia Haurat, Ph.D., Staff Fellow/LABORATORY OF BACTERIAL  
POLYSACCHARIDES/DIVISION OF BACTERIAL PARASITIC AND ALLERGENIC  
PRODUCTS/OFFICE OF VACCINES RESEARCH AND REVIEW**

**Lunhua Liu, Ph.D., Biologist/LABORATORY OF BACTERIAL  
POLYSACCHARIDES/DIVISION OF BACTERIAL PARASITIC AND ALLERGENIC  
PRODUCTS/OFFICE OF VACCINES RESEARCH AND REVIEW**

**Kathryn Matthias, Ph.D., Biologist/LABORATORY OF BACTERIAL  
POLYSACCHARIDES/DIVISION OF BACTERIAL PARASITIC AND ALLERGENIC  
PRODUCTS/OFFICE OF VACCINES RESEARCH AND REVIEW**

**1. BLA#: STN 125819****2. APPLICANT NAME AND LICENSE NUMBER**

GlaxoSmithKline Biologicals SA. License 1617

**3. PRODUCT NAME/PRODUCT TYPE**

Meningococcal Group ABCWY Vaccine, PENMENVY

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

- a. Vaccine
- b. Suspension for injection following reconstitution of a single-dose vial of lyophilized MenACWY vaccine component with the accompanying pre-filled syringe of MenB vaccine component.
- c. Each dose includes *N. meningitidis* capsular serogroup A, C, W, and Y polysaccharides at 10, 5, 5, 5 µg, respectively; serogroup B recombinant proteins (rp961c [NadA], rp287-953 [NHBA], and rp936-741 [fHbp]) at 50 µg each; 25 µg outer membrane vesicles.
- d. Intramuscular injection
- e. 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**

- a. Acknowledgement Letter – 26 February 2024
- b. First Committee Meeting – 07 March 2024
- c. Filing Meeting – 29 March 2024
- d. Mid-Cycle Meeting – 19 August 2024
- e. Late-Cycle Meeting – NA; GSK cancelled the meeting
- f. Request for reference product designation received 15 February 2024 – CBER's reference product determination board had not yet met to discuss the application at the time of finalization of the CMC memo. If approved by the board, the product will be designated as a reference product and the associated exclusivity periods will be based on the date of first approval.
- g. PDUFA Action Due Date – 14 February 2025

**6. CMC/QUALITY REVIEW TEAM**

<b>Reviewer/Affiliation</b>	<b>Section/Subject Matter</b>
Marcos Battistel, Ph.D. OVRP/DBPAP/LBP	<b>2.2 Introduction</b> <b>2.3 Quality Overall Summary:</b> <b>2.3.S:</b> Drug substance intermediates: MenA, MenC, MenW, MenY and CRM197 Drug Substances: MenA-, MenC-, MenW- and MenY-CRM <b>2.3.P:</b> MenACWY Lyo MenABCWY <b>2.3.A Appendices:</b> Adventitious Agents MenACWY Lyo <b>2.3.R-Regional Information</b> <b>3.2.S Drug Substances:</b> Drug substance intermediates: MenA, MenC, MenW, MenY and CRM197 Drug Substances: MenA-, MenC-, MenW- and MenY-CRM <b>3.2.P Drug Products:</b> MenACWY Lyo MenABCWY <b>3.2.A.2:</b> Adventitious Agents Safety Evaluation <b>3.2.R-Regional Information:</b> Pertinent CMC-related documentation for MenACWY conjugates, MenACWY Lyo DP, and MenABCWY DP
Maria Florencia Haurat, Ph.D. OVRP/DBPAP/LBP	<b>2.2 Introduction</b> <b>2.3 Quality Overall Summary:</b> <b>2.3.S:</b> RP287-953, RP936-741, RP961c, and OMV <b>2.3.P:</b> rMenB/OMV NZ (MenB Liquid) <b>2.3.A Appendices:</b> Adventitious Agents MenB Liquid <b>2.3.R Regional Information</b> <b>3.2.S Drug Substances:</b> RP287-953, RP936-741, RP961c, and OMV <b>3.2.P Drug Product:</b> MenB Liquid <b>3.2.A.2:</b> Adventitious Agents Safety Evaluation <b>3.2.R-Regional Information:</b> Pertinent CMC-related documentation for MenB DS, MenB Liquid DP
Lunhua Liu, Ph.D. OVRP/DBPAP/LBP	<b>3.2.P.5.2 Analytical Procedures:</b> Relative Potency by (b) (4) <b>3.2.P.5.3 Validation of Analytical Procedures:</b> (b) (4)

Kathryn Matthias, Ph.D.  OVRR/DBPAP/LBP	<b>Module 4 (refer to Integrated Review memo):</b>  4.2.1.1 Primary Pharmacodynamics  4.2.3.2–4.2.3.5, as pertains to immunogenicity analyses  <b>Module 5:</b>  5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies  5.3.5 Reports of Efficacy and Safety Studies (as related to serology endpoints)
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## 7. INTER-CENTER CONSULTS REQUESTED

No inter-center consults were requested.

## 8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
15 February 2024	Original Submission (STN 125819/0)	Reviewed by MB, MH, LL, and KM
03 May 2024	Response to IRs sent 22 April 2024 (STN 125819/0.4)	Reviewed by MB and MH
07 May 2024	Additional responses to IRs sent 22 April 2024 (STN 125819/0.7)	Reviewed by MB and MH
08 Jul 2024	Responses to IRs sent 25 Jun 2024 (STN 125819/0.13)	Reviewed by MB and MH
10 Jul 2024	Response to IR sent 21 Jun 2024 (STN 125819/0.14)	Reviewed by LL
26 Jul 2024	Updated batch analyses tables per 8 July 2024 agreement (STN 125819/0.15)	Reviewed by MB and MH
31 Jul 2024	Additional responses to IRs sent 25 Jun 2024 (STN 125819/0.17)	Reviewed by MB
12 Aug 2024	Responses to IRs sent 27 Jul 2024 (STN 125819/0.21)	Reviewed by MB
14 Aug 2024	Responses to IRs sent 02 Aug 2024 (STN 125819/0.22)	Reviewed by MB
30 Aug 2024	Additional responses to IRs sent 25 Jun 2024 (STN 125819/0.25)	Reviewed by MH
03 Sep 2024	Response to IRs sent 21 Aug 2024 (STN 125819/0.26)	Reviewed by LL
27 Sep 2024	Additional response to IRs sent 21 Jun 2024 (STN 125819/0.28)	Reviewed by LL
15 Oct 2024	Response to IRs sent 30 Sep 2024 (STN 125819/0.33)	Reviewed by MB
24 Oct 2024	Response to IRs sent 10 Oct 2024 (STN 125819/0.34)	Reviewed by MB
31 Oct 2024	Additional responses to IRs sent 30 September 2024 (STN 125819/0.36)	Reviewed by MB
04 Nov 2024	Responses to IRs sent 28 October 2024 (STN 125819/0.37)	Reviewed by MH

08 Nov 2024	New qualification data for reference standard and internal control batches, per STN 125819/0.13 (STN 125819/0.38)	Reviewed by MB
12 Nov 2024	New reference standard lot for (b) (4) (STN 125819/0.40)	Reviewed by LL
12 Nov 2024	Responses to IR comments 2 and 3 (statistical) sent 31 October 2024 (STN 125819/0.41)	Reviewed by statistical team
14 Nov 2024	Response to IR comment 1 sent on 31 October 2024 (STN 125819/0.43)	Reviewed by MB
14 Nov 2024	Updated stability data per commitments made in response to IRs sent on 25 June 2024, 25 July 2024, 17 August 2024, 30 September 2024, and 10 October 2024 (STN 125819/0.44)	Reviewed by MB, LL, and MH
09 Dec 2024	Response to IR sent on 27 November 2024 regarding MenACWY Lyo shelf life (STN 125819/0.51)	Reviewed by MB
10 Dec 2024	Response to IR sent on 02 December 2024 regarding MenA-CRM total and conjugate saccharide release specifications (STN 125819/0.53)	Reviewed by MB
15 Jan 2025	Updated Module 2 documents to reflect changes made based on IRs over the review cycle (STN 125819/0.61)	Reviewed by MB and MH
21 Jan 2025	Response to Carton and Container IRs (STN 125819/0.64)	Reviewed by MB
22 Jan 2025	Updated Sections 3.2.P.8.2 <i>Stability Monitoring Commercial Lots</i> (MenACWY-Lyo and MenABCWY) to reflect additional 18-month testing timepoints for (b) (4) stability monitoring due to MenACWY Lyo 18-month shelf life (STN 125819/0.65)	Reviewed by MB
23 Jan 2025	Response to USPI IRs (STN 125819/0.67)	Reviewed by MB
07 Feb 2025	Response to IR regarding reporting category for comparability protocols (STN 125819/0.71)	Reviewed by MB
10 Feb 2025	Response to IR clarifying definition of date of manufacture for determining expiry date (STN 125819/0.73)	Reviewed by MB

## 9. Referenced REGULATORY SUBMISSIONS (e.g., IND BLA, 510K, Master File, etc.)

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
STN 125300	GSK	MENVEO	No	CMC- and serology-related information in the original BLA and post-approval manufacturing supplements from throughout the MENVEO lifecycle; all relevant information is also present in STN 125819 (MB)
STN 125546	GSK	BEXSERO	No	CMC- and serology-related information in the original BLA and post-approval manufacturing supplements from throughout the BEXSERO product life cycle; all relevant information is also present in STN 125819 (MH)
IND 11278	GSK	MENVEO	No	Pharmacology and Toxicology data (in association with pre-clinical immunogenicity studies), and qualification/validation data for serological assays (KM)
IND 11561	GSK	BEXSERO	No	Pharmacology and Toxicology data (in association with pre-clinical immunogenicity studies), and qualification/validation data for serological assays (KM)
IND 14605	GSK	PENMENVY	No	CMC-related information (MB and LL); Pharmacology and Toxicology data (in association with pre-clinical immunogenicity studies), and qualification/validation data for serological assays (KM)
IND 27269	GSK	MenACWY-7B	No	Serology-related information (KM)
DMF (b) (4)	(b) (4)	(b) (4)	Yes	Authorization for FDA to reference the DMF for (b) (4)

## 10. REVIEWER SUMMARY AND RECOMMENDATION

### A. EXECUTIVE SUMMARY

GlaxoSmithKline Biologicals (GSK) is seeking licensure of PENMENVY, also termed MenABCWY vaccine, a pentavalent meningococcal conjugate vaccine indicated for active immunization of individuals 10 through 25 years of age to prevent invasive disease caused by *Neisseria meningitidis* serogroups A, B, C, W, and Y. PENMENVY is a Meningococcal Groups A, B, C, W and Y vaccine that consists of two Drug Product components to be combined before administration:

- **The Lyophilized MenACWY Drug Product component (DP, referred to herein as MenACWY Lyo):** A lyophilized powder supplied in a vial containing four *Neisseria meningitidis* oligosaccharides generated from the capsular polysaccharides (PS) of serogroups A, C, W, and Y (MenA, MenC, MenW, MenY respectively), each one separately activated and conjugated to CRM197 protein resulting in four drug substances (DS): MenA-CRM, MenC-CRM, MenW-CRM and MenY-CRM. Each of the DS intermediates (MenA, MenC, MenW, MenY, and CRM197) and each of the four DS that constitute MenACWY Lyo DP are identical to that of MENVEO (STN 125300).
- **The Liquid MenB DP component (referred to herein as MenB Liquid):** A suspension for injection supplied in a pre-filled syringe (PFS) containing three recombinant protein antigens derived from the *N. meningitidis* serogroup B strains (produced in *Escherichia coli* cells by recombinant DNA technology), and Outer Membrane Vesicles (OMV) purified from *N. meningitidis* serogroup B.

The MenACWY Lyo component is reconstituted with the MenB Liquid component immediately before administration.

To produce the MenACWY Lyo component, GSK grows *N. meningitidis* and purifies the capsular polysaccharides for conjugation to CRM197. CRM197 is a non-toxic form of the *Corynebacterium diphtheriae* Cross-Reactive Protein, (b) (4)

(b) (4) GSK produces CRM197 by growing *C. diphtheriae* strain (b) (4) and purifying the protein using chromatography (b) (4). They produce the PS intermediates after (b) (4)

(b) (4) The manufacturing processes for the PS and CRM197 intermediates, as well as the conjugate DS, are the same as for the U.S.-licensed vaccine MENVEO (STN 125300). The MenACWY Lyo DP component is formulated by (b) (4)

To produce the MenB Liquid DP component, GSK combines three recombinant MenB proteins and MenB OMV. The three MenB proteins are recombinantly expressed individually from *E. coli* containing plasmids with the genetic sequences of each protein (b) (4). The proteins include truncated Neisseria adhesin A (NadA; termed rp961c); a fusion protein comprising Neisseria heparin binding antigen (NHBA) and its accessory protein 953 (termed rp287-953); and a fusion protein comprising protein 741 (also called Factor H binding protein (fHbp)) and accessory protein 936 (termed rp936-741). The OMV are complexes that include outer membrane proteins, (b) (4). The outer membrane proteins, including the highly expressed PorA, are the primary antigens of the OMV. GSK manufactures the (b) (4) the recombinant *E. coli*, (b) (4)

(b) (4)

The MenB Liquid DP component is formulated by (b) (4) aluminum hydroxide (b) (4), followed by aseptic filling into washed, (b) (4), depyrogenated, and sterilized Type<sup>(b)</sup> glass syringes. The MenB Liquid composition and manufacturing processes are identical to BEXSERO (STN 125546), except that MenB Liquid includes (b) (4).

The PENMENVY final DP is a package containing one each of the MenACWY Lyo and MenB Liquid DP components. The product is generated by reconstituting the MenACWY Lyo DP with the entire contents of the MenB Liquid PFS. The reconstituted final DP is then drawn back up into the PFS for administration to the patient.

The PS and CRM197 are produced at GSK Vaccines S.r.l in Socioville, Italy (Rosia). CRM197 quality control testing is performed at GSK's facility in (b) (4). The conjugate DS are also produced at Rosia. The MenB recombinant protein DS are produced at (b) (4) and at Rosia. MenACWY Lyo DP is formulated and filled at GSK's facility in (b) (4). MenB Liquid DP is formulated and filled at Rosia. The MenABCWY Final DP is packaged at Rosia.

GSK developed in-process and release tests for the manufacture of the DS Intermediates, DS, DP components, and Final DP and validated them appropriately. The testing adequately measures quality and safety. GSK has incorporated some of the release tests into their stability testing programs for intermediates, DS, and DP. The hold times incorporated in the manufacturing processes are supported by validation data.

The PS DS intermediates are stored at (b) (4), and stability data support shelf lives of (b) (4) (MenA, MenW, and MenY) and (b) (4) (MenC and CRM197). The MenA-, MenC-, MenW-, and MenY-CRM conjugate DS are stored at (b) (4) (MenA-CRM, MenC-CRM, and MenY-CRM) and for



(b) (4) (MenW-CRM), which are the same storage parameters as for MENVEO. The three recombinant MenB protein DS are stored at (b) (4) with a shelf life of (b) (4), and the OMV DS is stored at (b) (4) with a shelf life of (b) (4). These storage conditions and shelf lives are identical to those for BEXSERO. GSK provided data to support assigning MenACWY Lyo DP expiry of 18 months and the MenB Liquid DP expiry of 48 months when stored at 2–8°C. Since the MenABCWY Final DP comprises two independent DP packaged together, the expiry date of each sale package is based on the earliest expiring component (i.e., either MenACWY Lyo or MenB Liquid) and is stored at 2–8°C. Upon reconstitution, the combined MenABCWY is to be administered immediately.

To demonstrate immunogenicity of the reconstituted PENMENVY DP, GSK first conducted pre-clinical studies in mice and rabbits. Serological readouts included total IgG antibody and functional antibody titers as measured in ELISAs and serum bactericidal activity assays (SBAs), respectively. The data suggested that the individual vaccine components were immunogenic, with overall enhanced seroresponses observed for animals immunized with three vs two vaccine doses (see comprehensive review in Section 5.1 *Nonclinical Assessment of Potential Effectiveness* of the CBER Integrated Review memo). GSK evaluated similar dosing regimens in the pivotal Phase 3 clinical study V72\_72, with immunogenicity of the MenB vaccine components assessed using a tilt human complement SBA (hSBA) and responses to the MenACWY components assessed via agar overlay hSBAs and an (b) (4) assay; vaccine effectiveness (or breadth of vaccine coverage) was measured using an endogenous complement hSBA (enc-hSBA).

In the enc-hSBA, clinical serum samples are collected and stored at -80°C to preserve the activity of the study participants' complement. The individual's complement and antibodies function together to induce bactericidal activity, which is tested against a (b) (4) complete 110-strain panel of invasive MenB disease isolates. The results of the enc-hSBA permit analysis of the breadth of coverage of vaccine responses compared among different vaccine groups and dosing regimens. In contrast, the anti-MenB tilt hSBAs and anti-MenACWY agar overlay hSBAs measure immunogenicity against a select panel of four MenB and (b) (4) MenACWY strains, where responses against each strain represent elicitation of functional antibodies to one of the primary vaccine antigens. Because the MenB vaccine components comprise protein antigens which are frequently expressed by serogroup MenACWY strains, GSK performed supplemental testing of clinical sera via the ECL assay to calculate anti-MenACWY IgG titers. By determining total IgG antibody concentrations, GSK was able to confirm immunogenicity to the MenACWY vaccine components and to assess whether anti-MenACWY hSBA titers were due predominantly to elicitation of anti-MenACWY antibodies or to cross-reactive anti-MenB antibodies.

GSK provided sufficient data to show the assays were suitable for their intended purposes, i.e., assessment of serological responses to PENMENVY and comparator vaccines in clinical trials V72\_72 and MENABCWY-019. The assays were validated and/or qualified at the laboratories at which clinical sample testing was carried out, demonstrating the ability of the on-site staff to perform the assays. GSK submitted

additional data to support stability of the assays between the time of assay validation or qualification and the clinical sample testing period, indicating that the assays were performing adequately to permit clinically meaningful differences among study groups.

## B. RECOMMENDATION

### I. APPROVAL

#### DS and DP Manufacturing Facilities

Manufacturer	Roles
GSK Vaccines S.r.l. Bellaria-Rosia 53018 Sovicille Italy	(b) (4) : Manufacture, storage, and testing <b>Polysaccharide intermediates and CRM197</b> : Manufacture, storage, and release testing <b>Conjugate DS</b> : Manufacture, storage, and release testing <b>MenB DS</b> : Manufacture, storage, and release testing
GSK Vaccines S.r.l. (b) (4)	(b) (4) storage (backup) CRM197 quality control testing
(b) (4) GlaxoSmithKline Vaccines (b) (4)	MenACWY Lyo warehousing operations
(b) (4)	MenACWY Lyo warehousing operations
(b) (4)	MenACWY Lyo warehousing operations

#### Comparability Protocols

The BLA includes the following comparability protocols:

*Previously approved protocols:*



**II.SIGNATURE BLOCK**

<b>Reviewer/Title/Affiliation</b>	<b>Concurrence</b>	<b>Signature and Date</b>
Marcos D. Battistel, Ph.D. Biologist CBER/OVRR/DBPAP/LBP	Concur	
Maria Florencia Haurat, Ph.D. Staff Fellow CBER/OVRR/DBPAP/LBP	Concur	
Lunhua Liu, Ph.D. Biologist CBER/OVRR/DBPAP/LBP	Concur	
Kathryn Matthias, Ph.D. Biologist CBER/OVRR/DBPAP/LBP	Concur	
Willie F. Vann, PhD Chief CBER/OVRR/DBPAP/LBP	Concur	
Jay E. Slater, MD Director CBER/OVRR/DBPAP	Concur	

## Review of CTD

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**Module 3****3.2.S DRUG SUBSTANCE INTERMEDIATES (Reviewed by MB)**

**Reviewer Comment:** In Section 1.2 Note to Reviewer CMC Addendum, GSK states that they did not perform any development for the DSI and DS of MenABCWY and that to manufacture MenACWY Lyo and MenB Liquid DP they used the available MENVEO and BEXSERO (b) (4) batches at the time of production. Therefore, the DS and DSI in MenABCWY are identical to those in MENVEO and BEXSERO, which were reviewed under their respective STNs (see STN 125300/0 CMC review memorandum dated 17 February 2010 and STN 125546/0 CMC review memorandum dated 23 January 2015, respectively). However, because of approved changes introduced during each product's life cycle and because data in the respective BLAs are relevant for MENVEO and BEXSERO but may not be relevant for MenABCWY (e.g., manufacturing changes introduced during MENVEO or BEXSERO clinical development), GSK divided the submitted information into four categories:

- **Identical:** no changes with respect to the information contained in MENVEO/BEXSERO.
- **Reformatted:** Editorial changes without any change to the technical content.
- **Customized:** Removed/added information not pertinent/pertinent to MenABCWY development; added up-to-date stability data, added additional text to improve clarity, added document references, and introduced editorial changes.
- **New:** Stand-alone sections to provide additional data pertinent to MenABCWY.

GSK provided for each DSI and DS a table (Table 1) summarizing the changes they introduced to each subsection within Module 3 as an Annex to Section 1.2 Cover Letters:

Annex 1, MenA; Annex 2, MenC; Annex 3, MenW; Annex 4 MenY; Annex 5, CRM197; Annex 6, MenA-CRM; Annex 7, MenC-CRM; Annex 8, MenW-CRM and Annex 9, MenY-CRM. The reported changes to the contents of each section relative to the respective DS and DSI sections in MENVEO fall under each of the four categories described above.

Therefore, my review of Module 3 regarding the MenACWY DSI and DS focuses on changes introduced to the documentation compared to the content of the MENVEO BLA and not on the processes that were previously reviewed for the already-licensed product.

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

### 3.2.P DRUG PRODUCT - MenACWY Lyo (Reviewed by MB)

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

MenACWY Lyo is formulated to contain 10 mcg/dose of MenA-CRM DS and 5 mcg/dose each of MenC-CRM, MenW-CRM, and MenY-CRM as active ingredients, and (b) (4) mg/dose of sucrose, (b) (4) potassium phosphate buffer (b) (4) as excipients. Because MenACWY Lyo is supplied as a powder in a 3-mL Type (b) (4) glass vial (with a 13-mm bromobutyl rubber stopper and aluminum flip-off cap), GSK applies a (b) (4) to ensure that the intended amount of each active ingredient is delivered when reconstituted with the MenB Liquid DS.

#### 3.2.P.2 Pharmaceutical Development

##### 3.2.P.2.1 Components of Drug Product - MenACWY Lyo

The MenACWY Lyo DP's active ingredients are the capsular polysaccharides (CPS) from serogroups A, C, W, and Y separately conjugated to CRM197 carrier protein. The polysaccharide-CRM197 conjugate manufacturing processes are described in each DS's Section 3.2.S.2.2 *Description of Manufacturing Process*, above.

##### 3.2.P.2.2 Drug Product

###### 3.2.P.2.2.1 Formulation Development

GSK states that they developed the formulation for MenACWY Lyo DP based on MENVEO (STN 125300). They indicate that during the initial development stages only the two-component MENVEO presentation was available (MenA-CRM lyophilized + MenCWY liquid); in 2022 we approved the MenACWY liquid presentation (STN 125300/778, approved 14 October 2022). In Table 1, GSK presents the formulation changes between Phase 1/Phase 2 and Phase 3/PPQ/post-PPQ MenACWY Lyo batches. The only formulation difference between early development stages and from Phase 3 onwards is how they (b) (4) For Phase 1/2 GSK (b) (4)

are the same.

###### 3.2.P.2.2.2 Overages

GSK uses a (b) (4) to ensure the required amount of MenACWY Lyo is reconstituted with MenB liquid prior to injection.

###### 3.2.P.2.2.3 Physicochemical and Biological Properties

The MenACWY Lyo component contains the same antigens in the same amounts as MENVEO (STN 125300) but in a fully lyophilized form (MENVEO has two presentations: one in which the MenA-CRM197 component is lyophilized and the other three are combined in liquid form, and one where the DP (i.e., all four DS conjugates) is fully

liquid). The MenACWY Lyo component is intended to elicit an immune response to the MenA, MenC, MenW, and MenY PS.

**Reviewer comment (MB):** *I review the MenACWY Lyo physicochemical properties under Section 3.2.P.5.1 Control of Drug Product and subsections therein, below (page 119 of this memo).*

### 3.2.P.2.3 Manufacturing Process Development

As described in Section 3.2.P.2.2.1 *Formulation Development* above, the only difference between early development stages and post-PPQ/commercial MenACWY Lyo lots is how GSK prepared (b) (4). Therefore, the composition of the MENVEO presentation and MenACWY Lyo are equivalent. However, the MENVEO all-liquid presentation does not contain sucrose (not needed as it is supplied in liquid form instead of lyophilized). These differences in component composition are summarized in section 3.2.P.2.3, Table 1.

The MenACWY Lyo manufacturing process consists of the following general steps:

- (b) (4)

**Reviewer comment (MB):** *The manufacturing process was different for each phase of development. Below I describe the process changes between development phases and the studies conducted to demonstrate product comparability.*

(b) (4)

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

- (b) (4)

**Table 21: Release and Characterization Tests to compare Phase (b) (4) MenACWY Lyo DP batches.**

Test	Acceptance Criteria	Results (Phase 2 and Phase 3 Batches <sup>a</sup> )
Appearance (before and after reconstitution)	White to white-off cake, clear, colorless, or slightly yellow	Conform
Identity	Positive	Conform
<b>Visible Particles</b>	<b>Free of visible particles</b>	<b>Conform</b>
(b) (4)	(b) (4)	Conform
Total Saccharide	(b) (4) mcg/vial (MenA) (b) (4) mcg/vial (each, MenC, MenW, and MenY)	Conform

Test	Acceptance Criteria	Results (Phase 2 and Phase 3 Batches <sup>a</sup> )
Free Saccharide	(b) (4) (MenA) (b) (4) each for other serogroups	Conform
Conjugate Saccharide	Target development ranges (b) (4) (MenA) (b) (4) (each, MenC, MenW, and MenY)	Conform
(b) (4)	Report Results	NA
(b) (4)		Conform
(b) (4)	Report Results	NA
Residual Moisture	(b) (4)	Conform
(b) (4)	(b) (4)	Conform
Endotoxin	(b) (4)	Conform
Sterility	Sterile	Conform
Pyrogenicity	Not Pyrogenic	Conform
Total Protein	(b) (4)	Conform
Sucrose	(b) (4)	Conform

<sup>a</sup> For tests shown in bold font, the results are for Phase (b) (4) batches only. <sup>b</sup> (b) (4). <sup>c</sup> Used for Phase (b) (4) release and Phase (b) (4) characterization (since implementation of (b) (4)). <sup>d</sup> GSK changed the MenA FS in MenACWY Lyo acceptance criterion in amendment 36 in response to our 10 October 2024 IR.

NA, not applicable due to specification of "report results"; (b) (4)

While not presented as part of their comparability assessment, GSK did perform Pyrogenicity testing for release on Phase (b) (4) and Phase (b) (4) batches. All the results for all batches are similar and conform to the respective acceptance criteria.

### Phase 3 Clinical Material and PPQ/Commercial Lot process changes (within (b) (4) commercial manufacturing facility, (b) (4) :

In preparation for commercial production GSK manufactured PPQ batches after implementing the following manufacturing changes:

- (b) (4)



- (b) (4)

GSK also performed a comparability study to support comparability of Phase 3 and PPQ lots. My review of the MenACWY Lyo DP PPQ, as well as this comparability-supporting documentation, can be found under memo Section 3.2.P.3.5 Process Validation and/or Evaluation, below (page 115 of this memo).

#### **MenACWY Lyo PPQ vs post-PPQ/commercial lots**

Although GSK did not report direct changes to the MenACWY Lyo DP process after performing PPQ, they did introduce process changes for MENVEO (STN 125300) that would impact MenACWY Lyo commercial batches. When we approved all those changes in the context of MENVEO we did not request data collected on MENVEO DP batches to support that the changes had no impact on product quality, as data generated with either DSI or DS batches were sufficient to support the changes.

**Reviewer comment (MB):** GSK notified us of the proposed process changes they intended to introduce for commercial MenACWY Lyo manufacturing in IND 14605 amendments 202, 215, and 236. For my review of those amendments please see my review memos dated 31 October 2022, 27 February 2023, and 26 January 2024, respectively. Although we did not require MENVEO DP data for the process changes in the respective MENVEO supplements, we considered it appropriate for GSK to produce a post-PPQ MenACWY Lyo batch to demonstrate no product impact. Our reasoning was that, compared to MENVEO, introducing multiple process changes could have an unexpected effect on MenACWY Lyo DP product quality that can be accentuated in the lyophilized product impacting not only the product at release but also its stability profile. In Section 3.2.P.2.3 Manufacturing Process Development (b) (4)

for all Phase 3, PPQ, and post-PPQ batches. The reported results are similar between batches and within the respective acceptance ranges.

GSK concludes that they consider PPQ and post-PPQ batches representative of commercial production because they were produced with the same process. I

*present my evaluation of MenACWY Lyo DP Phase 3, PPQ, and post-PPQ comparability beginning on page 116 of this memo, after I review all the pertinent sections under MenACWY Lyo DP.*

### **Product Control Strategy Overview**

GSK states that they defined their product control strategy (PCS) based on knowledge on the product, process, and analytics:

- The definition of DP CQAs and associated acceptance criteria, which focus on the product and its quality.
- Defining and categorizing PPs and their acceptability ranges, which focus on the process and its performance:
  - Manufacturing PP (those that impact performance attributes, PAs).
  - Critical process parameters (CPP, those that impact either CQAs or CQAs and PAs).
  - PPs, which do not impact CQAs or PAs.

GSK defined Quality Attributes based on their potential impact on product safety/and or efficacy and PAs based on product yield impact. Once they identified initial CQAs and PAs they performed a technical risk assessment. Further, GSK states that their control strategy is dynamic as it is modified as they gain more knowledge during the vaccine lifecycle.

To ensure they maintain product quality and adequate process performance, and to gain product knowledge, the applicant performs a series of tests that they divide into the following categories:


- Quality decision (QD): IPCs whose results will determine if the process is continued or stopped. Therefore, the tests have associated *acceptance criteria*. *Quality Release tests* fall under this category, as batches that do not meet the acceptance criteria are discarded.
- Process monitoring: IPC tests performed at a given step to monitor process performance and consistency and to accumulate data for knowledge (i.e., for trending and root-cause analysis). These tests have associated alert limits.
- Characterization and process measurements or Manufacturing Control: GSK performs characterization tests to gain product knowledge. Although these tests do not have associated acceptance criteria, their results can be used to assess comparability of batches, to prompt further investigation, or to evaluate if the tests should be included in the release or release/stability testing panels. These tests encompass product physicochemical and immunological properties as well as determination of levels of impurities and are normally applicable to a limited number of batches. GSK performs manufacturing control tests to adjust the process based on test results (e.g., <sup>(b) (4)</sup> determination during <sup>(b) (4)</sup> ).

**Components of Drug Substance- Excipients-MenACWY Lyo**

GSK uses sucrose (as a lyophilization bulking agent and as a tonicity agent) and potassium phosphate (b) (4), as buffering agent).

**Manufacturing Process Development Overview**

(b) (4)

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(b) (4)

### 3.2.P.2.4 Container Closure System

#### Suitability

To evaluate the suitability of the container closure system during development GSK evaluated:

- Compatibility through long-term stability studies (Section 3.2.P.8.3 Stability Data\_MenACWY Lyo, page 150 of this memo).
- Protection from light, which is ensured via the secondary packaging.
- Container closure integrity, which GSK also evaluated during long-term stability studies.
- Safety through an E&L study (see Section 3.2.P.2.4 *Container Closure System - Safety Evaluation\_MenACWY Lyo* and *Container Closure System – Safety Evaluation, directly below*).

#### Safety Evaluation

**Reviewer comment (MB):** GSK describes the container closure system in Section 3.2.P.7 *Container Closure System*. However, since they describe the E&L study in this section, I consider pertinent to also review container closure here.

The formulated and filtered MenACWY Lyo DP (b) (4) is filled in 3-mL Type (b) (4) glass supplied by either (b) (4)

(b) (4) All these vials are (b) (4) to facilitate reconstituted product extraction. The vial is sealed with a (b) (4) bromobutyl Type (b) (4) rubber stopper (b) (4) rubber stopper, supplied by (b) (4). The vial and the stopper are in contact with the product, therefore GSK performed E&L using both. The stopper is secured with a flip-off cap made of propylene to and aluminum cap.

(b) (4)

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

In Section 3.2.P.7 *Container Closure System-Vial Container*, GSK indicated they have three vial suppliers ((b) (4))

From the information GSK provided, it is not clear:

- if the vials from different suppliers are identical (same manufacturer) or if there are differences among them;
- if GSK used all three vials in the manufacture of MenACWY Lyo DP;
- if they tested compatibility with the DP with each of these vials (or enrolled DP batches using these three vials in long-term stability studies); or
- if they performed leachables studies using the three vials.

Therefore, we sent an Information Request on **25 June 2024** (comment 3) asking them to provide this information. GSK responded on 8 July 2024. Due to the lack of data to support the use of the vial supplied by (b) (4) GSK agreed to remove the use of the (b) (4) vial for MenACWY Lyo DP.

(b) (4)

provided up-to-date stability data, including (b) (4) test results, to support container closure suitability on 14 November 2024 (**Amendment 44**; see page 192).

### Overall Reviewer's Assessment of Section 3.2.P.2:

GSK provided data to demonstrate acceptable development activities for MenACWY Lyo DP. While we identified deficiencies regarding the (b) (4) assay, the (b) (4) assay for MenA, and the (b) (4) test, GSK adequately addressed our concerns in responses to our Information Requests. The extractables study did not identify any substances of concern and the leachables study is ongoing. GSK also removed use of the (b) (4) container closure for which they did not have adequate supportive data.

## 3.2.P.3 Manufacture

### 3.2.P.3.1 Manufacturer(s)

The following facilities are involved in manufacturing, testing, and warehousing of commercial MenACWY Lyo:

**Table 22: Manufacturers–MenACWY Lyo.**

Site Name/Address	Responsibility
GlaxoSmithKline Biologicals (b) (4)	Formulation, filling, lyophilization, quality control testing, visual inspection, and warehousing
GlaxoSmithKline Vaccines S.r.l. Bellaria-Rosia 53018 Sociville (SI) Italy	Quality control, stability testing, and warehousing
(b) (4)	Warehousing Operations
(b) (4)	Warehousing Operations
(b) (4)	Warehousing Operations

These facilities were also used for PPQ and post-PPQ batch production.

### 3.2.P.3.2 Batch Formula

(b) (4)



GSK will produce DP (b) (4) batches at (b) (4), depending on commercial demand. The final concentrations for active ingredients and excipients are the same, but the (b) (4)

**Overall Reviewer's Assessment of Sections 3.2.P.3.1 and 3.2.P.3.2:**

GSK provided adequate documentation to support the use of different (b) (4) for MenACWY Lyo DP spanning from (b) (4) (which I review under Process validation section 3.2.P.3.5 *Process Validation and/or Evaluation on page 115 of this memo*).

**3.2.P.3.3 Description of Manufacturing Process**

GSK first (b) (4)

. Therefore, we requested GSK provide clarification on **25 June 2024** (comment 9; see section beginning on page 156 of this memo).

(b) (4)

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

(b) (4)

**Overall Reviewer's Assessment of Section 3.2.P.3.3:**

Combining the documentation GSK provided in the original submission and that included in amendments 4, 13, and 21 (dated 3 May, 8 July, and 12 August 2024) GSK provided adequate documentation to support that their manufacturing process can produce MenACWY Lyo DP batches that conform to the proposed release acceptance criteria set for all the defined critical quality attributes. Please refer to Information Request Letters for MenACWY Lyo DP review section of this memorandum for all the communications with GSK and my review of GSK's responses.

**3.2.P.3.4 Controls of Critical Steps and Intermediates**

There are no process intermediates in the manufacturing of MenACWY Lyo DP.

GSK divides the in-process assays in two categories:

- Quality decision (QD) assays that are associated with acceptance limits, which GSK performs at critical decision-making steps. GSK uses these assays to ensure product quality and the manufacturability of the process.
- Process monitoring (PM) assays are associated with alert limits and GSK performs them to evaluate process consistency.

During formulation filling and lyophilization, GSK samples the product for (b) (4)

*Bioburden assay:*

Description: GSK tests the samples by (b) (4)

Assay Validation: To evaluate any potential product impact of MenACWY Lyo on microorganisms' growth, GSK (b) (4)


*Batch analysis data for QD assays:*

(b) (4) and post-PPQ lots (b) (4) All batches (b) (4) acceptance criterion (b) (4) detected).

The data GSK included in this section are adequate. I did not identify deficiencies.

**3.2.P.3.5 Process Validation and/or Evaluation**

(b) (4)



I



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**Overall Reviewer's Assessment of Section 3.2.P.3.5:**

In response to our IRs sent on 25 June and 2 August 2024, GSK provided additional data to adequately address our concerns (**STNs 125819/0.13** and **125819/0.22**, respectively). For the communications sent to GSK and my review of GSK's responses please refer to the Information Request Letters for MenACWY Lyo review section of this memo, starting on page 156. The information provided is acceptable and GSK has adequately validated their manufacturing process.

**3.2.P.4 Control of Excipients****3.2.P.4.1 Specifications**

*Sucrose and potassium (b) (4) phosphate*: Purchased from commercial suppliers and compliant with (b) (4).

<sup>(b) (4)</sup> *potassium phosphate*: Purchased from commercial suppliers and compliant with (b) (4).

**3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures**

The excipients are compliant with (b) (4), consistent with the documentation in STN 125300.

**3.2.P.4.4 Justification of Specifications**

Not applicable as the excipients are tested with (b) (4) methods.

**3.2.P.4.5 Excipients of Human or Animal Origin**

MenACWY Lyo does not include excipients of human origin.

**3.2.P.4.6 Novel Excipients**

Not applicable.

**Overall Reviewer's Assessment of Section 3.2.P.4:**

In this section GSK provided equivalent information as they provided for the same excipients used in MENVEO (b) (4). GSK indicates they test the excipients according to the current editions of the (b) (4) National Formulary. The information provided is 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)**

GSK performs the following assays:

**Table 23: Release and Stability Specifications for MenACWY Lyo DP.**

Attribute	Acceptance Criteria – Release	Acceptance Criteria – Stability	Test Method
Appearance (b) (4)	Cake: White to off white Reconstituted: Colorless to light yellow	Cake: White to off white Reconstituted: Colorless to light yellow	(b) (4)
Identity	FC: Positive for each conjugate saccharide FP: Positive for MenY-CRM		(b) (4)
Conjugate Saccharide—MenA-CRM	(b) (4)	(b) (4)	(b) (4)
Conjugate Saccharide—MenC-, MenW, and MenY-CRM	(b) (4)	(b) (4)	(b) (4)
MenA Total Saccharide	(b) (4)	(b) (4)	(b) (4)
MenC, MenW, and MenY Total Saccharide	(b) (4)	(b) (4)	(b) (4)
MenA Free Saccharide	(b) (4)	(b) (4)	(b) (4)
MenC, MenW, and MenY Free Saccharide	(b) (4)	(b) (4)	(b) (4)
Total Protein	(b) (4)	(b) (4)	(b) (4)
Sucrose Content	(b) (4)	(b) (4)	(b) (4)
Residual Moisture	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Visual Particles	Free from visible particles	Free from visible particles	Visible Inspection (b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sterility: (b) (4)	Absence of growth	Absence of growth	(b) (4)
Endotoxin	(b) (4)	(b) (4)	(b) (4)



<sup>a</sup> Acceptance criteria updated in Amendment 36 dated 31 October 2024. <sup>b</sup> Acceptance criteria updated in Amendment 33 dated 15 October 2024. <sup>c</sup> Acceptance criteria updated in Amendment 17 dated 31 July 2024.

(b) (4); FC, final container;  
FP, final pack; (b) (4)

GSK provided the following justifications for the specifications they set for release and stability:

- Appearance (Visual Inspection): The assay is required by (b) (4)
- Identity (by (b) (4)): GSK performs the assay at both final container and final pack stages to ensure the product contains the active ingredients. The assay is required by (b) (4). While they test for all four conjugates at final container stage, GSK (b) (4).  
(b) (4) GSK manufactures two lyophilized products (MenA Lyo and MenACWY Lyo); the other DP component from MENVEO is in liquid form (i.e., MenCWY Lyo). Thus, if the lyophilized cake is positive for MenY-CRM, it confirms the correct product (MenACWY Lyo and not MenA Lyo).
- Conjugate Saccharide (CS, by (b) (4)): GSK set the acceptance criteria based on their experience with FS and TS tests results from MENVEO commercial batches (CS=TS-FS). Because the DP contains higher concentrations of MenA-CRM compared to MenC-, MenW-, and MenY-CRM, they set different acceptance criteria for release/stability (see table above). GSK set the lower limit for the assay assuming no FS for each serogroup and the upper limit based on the worst FS concentration for each serogroup. The limits GSK set are consistent with those from TS and FS from MENVEO.
- Total and Free Saccharide (TS and FS by (b) (4)): GSK also set the acceptance criteria based on their experience with MENVEO. Although GSK determines TS and FS, only FS is stability-indicating; however, TS is required to be able to determine FS content (% FS value from the TS). However, because for PPQ batches they also measured CS, TS can also be determined. The TS, FS, and CS are indicators of product quality and process consistency.
- Total Protein (by (b) (4)): GSK set the acceptance criterion based on the acceptance range for the (b) (4).  
(b) (4) acceptance criteria form which total protein range can be calculated.
- Sucrose content (by (b) (4)): GSK set the acceptance criterion based on the target range of (b) (4). The range was applied throughout their development of MenACWY Lyo. The firm found that product with sucrose contents within the acceptance range had appropriate appearance and adequate stability throughout the product's life cycle.

- Residual Moisture (by (b) (4)): GSK set the acceptance criterion based on pharmacopeial recommendations for lyophilized products (b) (4)
- (b) (4)
- Visible particles (by visual inspection): GSK performs the test according to (b) (4) and the results must indicate that the product is free of visible particles.
- (b) (4)

**Reviewer comment (MB):** GSK set the (b) (4) acceptance criterion of (b) (4) based on the results from (b) (4) Phase 3, PPQ, and post-PPQ batches, from which they calculated a one-sided tolerance limit that 99% of the measured values will fall within this limit with 95% confidence. However, the highest (b) (4) of a clinically tested Phase 3 batch was (b) (4) (batch (b) (4), 3.2.P.5.4 Batch Analyses Clinical Lots). The highest (b) (4) value measured for PPQ batches was (b) (4), but with most values falling below (b) (4) (batch (b) (4), 3.2.P.5.6 Justification of Specifications (b) (4)). Therefore, none of the batches studied approached the proposed upper acceptance criterion limit of (b) (4).

To ensure that future commercial batches have critical quality attributes consistent with clinically tested batches, the proposed acceptance criterion for (b) (4) should be set according to values measured for Phase 3 batches. However, when evaluating the proposed acceptance criterion one also must consider that the determined (b) (4) assay could contribute up to (b) (4) error in the measured value (Section 3.2.P.5.3 Validation of Analytical Procedures (b) (4) by (b) (4)). When considering a (b) (4) fluctuation in the result, the (b) (4) value reported for Phase 3 batch (b) (4) could have been (b) (4). Because the clinically tested batches yielded (b) (4) results than PPQ/post-PPQ batches (which reflect the commercial manufacturing process), and because the proposed acceptance criterion is consistent with CQA tested with clinical batches when taking into account the potential error in the measurement, I consider the acceptance criterion GSK set for (b) (4) to be adequate. Since the limited available PPQ/post-PPQ data support that the commercial process can consistently produce batches with (b) (4) as GSK gains commercial manufacturing experience, they may need to tighten

*the acceptance criterion to adjust to the most up-to-date manufacturing capability.*

- Sterility Test (by (b) (4) ): GSK performs the test according to (b) (4)  
The acceptance criterion confirms the sterility of the final container.
- Endotoxin (by (b) (4) Method): GSK derived the acceptance criterion of (b) (4) from current MENVEO acceptance criterion (the sum of MenA Lyo + MenCWY liquid permitted endotoxin content). The criterion is (b) (4)

#### **Overall Reviewer's Assessment of Sections 3.2.P.5.1 and 3.2.P.5.6:**

We requested GSK include the (b) (4) as part of the reported release and stability results for MenACWY Lyo DP because the average (b) (4), reported by the (b) (4) parameter, can directly impact the vaccine's immunogenicity (IR dated **25 June 2024**). GSK complied with our request. Furthermore, in response to IR #22 dated **30 September 2024**, GSK updated CS release and stability acceptance criteria for MenA-CRM (**STN 125819/0.36** dated 31 October 2024) as well as the release and stability acceptance criteria of FS and CS for MenC-, MenW-, and MenY-CRM (**STN 125819/0.33** dated 15 October 2024). Also, in response to IR #22, GSK included the (b) (4) test for release and stability monitoring of MenACWY Lyo DP batches with the corresponding acceptance criteria (**STN 125819/0.33** dated 15 October 2024). The release specifications and GSK's justifications are appropriate.

#### **3.2.P.5.2 Analytical Procedures and 3.2.P.5.3 Validation of Analytical Procedures**

The following analytical procedures and their validations were reviewed by the DBSQC; please refer to DBSQC memos for details on these analytical procedures and their validations: Appearance, Identity, Total Protein, Sucrose Content, Residual Moisture, (b) (4) Visible Particles, Sterility, and Endotoxin.

This section will focus on the following analytical procedures and their validations:

- (b) (4)

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

**Overall Reviewer's Assessment of Sections 3.2.P.5.2 and 3.2.P.5.3:**

GSK adequately demonstrated that the (b) (4), CS, and TS assays are adequate for their intended purpose. GSK also demonstrated that the test to measure MenW and MenY FS in MenACWY Lyo is adequate to be used for release and stability monitoring of MenACWY Lyo DP.

GSK did not demonstrate that the FS assays for MenA and MenC have adequate (b) (4) during the original assay validation. However, in response to our requests for information dated **30 September 2024**, the applicant provided (in **STN 125819/0.33** and **STN 125819/0.36** dated 15 October and 31 October, respectively) additional documentation and tightened the release and stability acceptance criteria for the MenACWY Lyo DP FS assay for all the serogroups, such that set acceptance criteria are now all consistent with the respective validated ranges for the FS assay. Furthermore, as a consequence of the revision GSK made for the FS assays, they also tightened the acceptance criterion for the CS content assay in MenACWY Lyo DP. Therefore, the assays are adequately validated for their intended use.

**3.2.P.5.4 Batch Analyses**

The applicant provided release data for their nonclinical/toxicology, Phase 1, Phase 2, Phase 3, PPQ, and post-PPQ batches. They also included release data for an engineering lot (b) (4) which they manufactured prior the PPQ runs.

- Non-clinical/toxicology batches: 002011 and S0002
- Phase 1: (b) (4)
- Phase 2: (b) (4)
- Phase 3: (b) (4)
- PPQ: (b) (4)
- Post-PPQ: (b) (4)

**Reviewer comment (MB):** All the batches conformed to the specifications set at the time of testing. The batch release information provided is acceptable.

With respect to the CS assay, all the release results conform to the respective acceptance criterion. However, since GSK implemented the assay in Phase (b) (4) I note that GSK produced PPQ and post-PPQ batches with higher CS content than those produced and tested for Phase (b) (4). Consistent with this observation is that I also note that total protein content for some PPQ batches and for the post-PPQ batch are higher than those batches tested clinically. A higher proportion of CS at the extent observed is not a reason of concern, because it does not reflect a sub-potent batch

and because a variability of (b) (4) is expected based on the method validation data.

### 3.2.P.5.5 Characterization of Impurities

There are no other process/product-related impurities other than those for the DS. GSK controls DP process- and product-related impurities through Endotoxin/Bioburden in-process controls and through Endotoxin and Sterility release assays.

#### **Overall Reviewer's Assessment of Sections 3.2.P.5.4 and 3.2.P.5.5:**

The release data for the batches presented are within specification with no concerning trends observed. The information presented sections 3.2.P.5.4 and 3.2.P.5.5 is acceptable. I did not identify any deficiencies.

### 3.2.P.6 Reference Standards or Materials

#### *Reference Standards*

GSK presents a list of qualified reference standards they use for the MenA-CRM CS, TS, and FS assays, MenC-CRM CS assay, and MenW-CRM and MenY-CRM CS, TS, and FS assays. These reference standards are DSI for each serogroup (b) (4) capsular polysaccharides from serogroups A, C, W, and Y). In Table 2, GSK includes links to the batch qualification report documents, for each of these batches, in Section 3.2.R *Regional Information*.

**Reviewer comment (MB):** *Though the reports are submitted under 3.2.R, I have included my review of these documents within this section.*

#### **MenA PS qualification:** (b) (4)

- (b) (4)

(b) (4)

. On **25 July 2024** (comment 7) we requested GSK to provide stability data for the reference standards demonstrating their adequacy for their intended purpose. GSK responded on 12 August 2024 providing the data we requested (see section beginning on page 171).



For MenC, MenW, and MenY standards qualification, GSK follows the same qualification procedure as for MenA standard; however, MenC <sup>(b) (4)</sup> is determined by (b) (4) method.

- (b) (4)





(b) (4)



### 3.2.P.7 Container Closure System

Please refer to Section 3.2.P.2.4 Container Closure System (page 107 of this memo) for review of the container closure.

#### Overall Reviewer's Assessment of Section 3.2.P.7:

The information provided in this section is acceptable. I found no deficiencies in section 3.2.P.7.

### 3.2.P.8 Stability


The stability assays GSK selected to monitor MenACWY Lyo DP stability are in line with those selected for MENVEO MenACWY liquid.

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

GSK proposed a 36 month of shelf life (Section 3.2.P.8.1 *Stability Summary and Conclusions*) based on the stability data from Phase 3, Engineering, PPQ and post-PPQ batches. They performed stability studies under the following conditions:

- Long-term stability for DP stored at 2–8°C. In the initial submission, GSK provided:

- (b) (4)



- Accelerated stability for DP stored at (b) (4)

○ (b) (4)

GSK provided additional stability data in **STN 125819/0.44**, reviewed below beginning on page 192.

The applicant evaluated data trending following ICH guidelines and internal procedures for performing stability analysis using (b) (4) software. To determine DP expiry GSK states that they will estimate, through statistical analysis from the available stability data, the earliest time point in which one of the parameters they monitor would fail the stability acceptance criterion with 95% confidence.

**Reviewer comment (MB):** *Their procedure may be adequate; however, my recommendation for DP expiry is based on the available data from DP batches produced from the most current process (PPQ and post-PPQ). For these batches there are still limited data to support a DP expiry of 36 months. On 14 November 2024 GSK provided the most-up to date stability data for MenACWY Lyo, MenB Liquid, and MenABCWY clinical, PPQ and post-PPQ batches. GSK reported out-of-trend MenA FS results for PPQ and post-PPQ batches and notified us that due to these results they had an open investigation to address the issue. Because the MenACWY Lyo post-PPQ batch out of trend MenA FS result of (b) (4) is close to the acceptance criterion limit of (b) (4) (at the latest time point they provided, i.e., 18 months) and because the post-PPQ batch is the most representative of commercial production, we recommended GSK set the MenACWY Lyo DP shelf life to 18 months until they close the investigation and provide supporting data for shelf-life extension (IR # 34, 27 November 2024). Please refer to my review of **STN 125819/0.44** (page 192) for more details. GSK responded on 9 December 2024 (**STN 125819/0.51**) complying with our request of setting MenACWY Lyo expiry to 18 months.*

GSK performs the following assays in their stability program (acceptance criteria in parenthesis):

**Assays that report on general product properties:**

- Appearance (White to off white/clear, colorless to light yellow when reconstituted)
- (b) (4)
- Visual inspection (free from visible particles)
- Residual moisture (b) (4)
- (b) (4)

**Assays that report on potency-related product properties:**

- Free saccharide (b) (4) for MenA and (b) (4) each for MenC, MenW and MenY). *In response to our requests for information dated 30 September 2024, GSK updated these acceptance criteria (STNs 125819/0.33 and 125819/0.36, respectively) from the previously proposed (b) (4) for MenA and (b) (4) each for MenC, MenW and MenY).*
- Total saccharide ((b) (4) for MenA and (b) (4) each for MenC, MenW and MenY)
- Conjugate saccharide ((b) (4) for MenA and (b) (4) each for MenC, MenW and MenY). *These acceptance criteria were updated on 15 and 31 October 2024 (STNs 125819/0.33 and 125819/0.36, respectively) from the previously proposed (b) (4) for MenA and (b) (4) each for MenC, MenW and MenY.*

**Assays that report on safety-related product properties:**

- Sterility (No growth/sterile)
- Container Closure Integrity Test (CCIT, (b) (4) )

Phase 3 clinical batches (b) (4)

Below I summarize the identified patterns in the provided stability data:

- Residual moisture: I note an (b) (4) (Section 3.2.P.8.3 *Stability Data Long-Term Phase 3 Clinical Lots*). However, the results remain well within the acceptance criterion of (b) (4). GSK explains that % Residual moisture (b) (4) in the first months of storage is a normal phenomenon and that residual moisture then (b) (4) at around (b) (4)

GSK performed a trend analysis in which they identified statistically significant trends for the following:

- (b) (4) GSK observed (b) (4) so the results remain well within the acceptance criterion (b) (4)
- Conjugate Saccharide: GSK identified an (b) (4) Consequently, we communicated our concern to GSK on 25 July 2024 (comment 8). GSK responded on 12 August 2024 (STN 125819/0.21), providing adequate information to demonstrate that the (b) (4) For more information, please refer to the section beginning on page 171.

**Reviewer comment (MB):** There are no concerning trends in the data of the Phase (b) (4) batches. The applicant did not report any out-of-specification (OOS) results. However, GSK introduced multiple manufacturing changes between Phase (b) (4) and PPQ. Therefore, it is not clear if the stability trends for Phase (b) (4) batches are representative of the PPQ/commercial MenACWY Lyo DP, and by extension, if they can be used to define commercial DP expiry.

MenACWY Lyo (b) (4)

GSK provided (b) (4) months of long-term stability data for this batch (Section 3.2.P.8.3 Stability data Long-Term – (b) (4))

**Reviewer comment (MB):** I do not observe concerning trends and GSK did not report any OOS results. I note, for Phase (b) (4) batches, (b) (4)

(b) (4)  
GSK responded on 14 August 2024 (STN 125819/0.22) complying to our request. Please refer to the review section beginning on page 179 of this memo for our requests for information and my review of GSK answers.

MenACWY Lyo DP PPQ lots:

GSK initially provided 18 months of stability data for batches (b) (4) and 12 months of stability data for (b) (4) (see STN 125819/0.44 (page 192) for details of the updated stability data provided in November 2024 and the associated review).

As noted for Phase (b) (4) batches, GSK reports (b) (4) trends for CS results for MenA-CRM (for all batches), MenC-CRM (batch (b) (4)), and MenW ((b) (4)) (Section 3.2.P.8.3 Stability Data Long-Term - PPQ Lots). They justify the observed trends are likely due to the variability between analytical sessions.

**Reviewer comment (MB):** As discussed for the CS assay of Phase (b) (4) lots, above, on 25 July 2024 (comment 8) we requested GSK to provide a justification of the trends we observe and notified them that if the (b) (4) trends continue in future stability time-points they (b) (4). GSK responded on 12 August 2024 (STN 125819/0.21) providing additional documentation that supports their conclusion that the apparent (b) (4) CS results is due to assay variability, and not an issue with

*stability, thus addressing our concerns. Please see the Information Requests section beginning on page 171 for more details.*

*MenACWY Lyo DP post-PPQ lot:*

GSK provided (b) (4) months of stability data for batch (b) (4).

**Reviewer comment (MB):** *Because the data are limited, I cannot perform a trend analysis on the data. However, all the provided data conform to the stability acceptance criteria. I note, however, that MenA FS content appears to have (b) (4) compared to results at release (Section 3.2.P.8.3 Stability data Long-Term – Post-PPQ Lot).*

*GSK provided updated stability data in STN 125819/0.44 (page 192). Please refer to this section for my review of these new data.*

### 3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment

In Section 3.2.P.8.2 *Post-Approval Stability Protocol and Stability Commitment Phase 3 Clinical Lots*, GSK commits to complete the stability study on Phase 3 MenACWY Lyo final container stored at 2–8°C for up to 48 months.

**Reviewer comment (MB):** *As discussed above, on 25 June 2024 we requested GSK to retain the (b) (4) assay to demonstrate to demonstrate no impact to this CQA occurs at release or during DP storage as a result of any future process change that they may propose to implement. GSK responded 8 July 2024 (STN 125819/0.13) complying with our requests.*

In Section 3.2.P.8.2 *Post-Approval Stability Protocol and Stability Commitment* (b) (4), GSK commits to complete the stability study on the (b) (4) MenACWY Lyo final container stored at 2–8°C for up to (b) (4) months following ICH guidelines. GSK does not include (b) (4) after (b) (4) months of storage. For the applicant to support the proposed 36-month expiry they should include all (b) (4)-derived parameters to support proposed DP expiry. On 25 June 2024, we asked GSK to retain all attributes they measure with the (b) (4) assay. GSK adequately addressed our concerns with STN 125819/0.13 dated 8 July 2024.

In Section 3.2.P.8.2 *Post-Approval Stability Protocol and Stability Commitment – PPQ Lots*, GSK commits to complete the stability study on PPQ MenACWY Lyo final container lots stored at 2–8 °C for up to (b) (4) months following ICH guidelines. They now include (b) (4) and (b) (4) attributes in the stability protocol.

In Section 3.2.P.8.2 *Post-Approval Stability Protocol and Stability Commitment Post-PPQ Lot*, and in Section 3.2.P.8.2 *Post-Approval Stability Protocol and Stability Commitment Stability Monitoring of Commercial Lots* GSK commits to complete the stability study on the enrolled post-PPQ batch and to enroll (b) (4) commercial MenACWY Lyo batch (b) (4) and perform the following assays annually for up to (b) (4) months:

- Appearance
- (b) (4)
- Residual moisture

- Visible particles by visual inspection
- Sterility
- CCIT
- CS
- TS/FS
- (b) (4)

count (as agreed in amendment 34 dated 24 October 2024)

On 22 January 2025, GSK submitted updated 3.2.P.8.2 *Post-Approval Stability Protocol and Stability Commitment Stability Monitoring of Commercial Lots* to reflect the addition of an 18-month testing timepoint, reflecting the 18-month MenACWY Lyo shelf life (**STN 125819/0.65**).

#### **Overall Reviewer's Assessment of Section 3.2.P.8:**

With one exception, I did not observe concerning trends in initial long term stability data for Phase (b) (4) PPQ, and post-PPQ batches in the data that was available prior to November 2024. The exception is the apparent (b) (4) CS results for MenY-CRM for Phase (b) (4) DP batches, but GSK provided adequate evidence to support the conclusion that the apparent CS results (b) (4) is due to analytical variability (**STN 125819/0.21**). However, GSK manufactured PPQ and post-PPQ after implementing multiple process changes approved for MENVEO (under STN 125300; described in IND 14605 amendments 202, 215, 236, and 251). Because GSK only had limited stability data (at most 18 months) for MenACWY Lyo DP manufactured using the most current process to support their requested 36-month expiry, the impact of these process changes on the stability of MenACWY Lyo DP was not fully known.

GSK submitted more up-to-date stability data for MenACWY Lyo Phase (b) (4) PPQ and post-PPQ batches on 14 November 2024 (**STN 125819/0.44**, see page 192 of this memo). GSK reported out-of-trend MenA FS results for PPQ and post-PPQ batches and notified us that due to these results they have an open investigation to address the issue. Because the out-of-trend MenA FS result for the MenACWY Lyo post-PPQ batch is close to the acceptance criterion limit of (b) (4) at the 18-month time point (most recent) and because the post-PPQ batch is the most representative of commercial production, we recommended GSK to set expiry to 18 months for the MenACWY Lyo DP until they close the investigation and provide supporting data for shelf-life extension (IR # 34, 27 November 2024). Please refer to my review of STN 125819/0.44 for more details. GSK responded on 9 December 2024 (**STN 125819/0.51**) complying with our request of setting the MenACWY Lyo expiry to 18 months. In **STN 125819/0.73** (10 February 2025) GSK clarified that expiry dating would be based on the filling date as date of manufacture.

**Information Request Letters for MenACWY Lyo DP Review**

For each Information Request, I have provided a brief synopsis of each comment followed by GSK's responses and my review.

**Information request letter 12 (dated 25 June 2024) and GSK responses review (amendments 13 and 17 dated 8 and 31 July 2024)****CBER Comment 1:**

*GSK refers to MenACWY Lyo and MenB Liquid as Drug Products. We felt this was not appropriate since they are not to be used separately (21 CFR 210.3 (4)). We requested GSK submit revised documents for MenACWY Lyo and MenB Liquid referring to them as Drug Substances instead of Drug Products and for the conjugate DS to be referred to as Drug Substance Intermediates.*

**GSK's Response to Comment 1:**

GSK stated that the nomenclature they use for PENMENVY is consistent with that used for MENVEO (also a co-packaged vaccine, with MenA lyophilized in a vial and MenCWY liquid in a pre-filled syringe) and that they do not consider MenACWY Lyo and the MenB Liquid as unformulated active ingredients, which is the definition of a Drug Substance. GSK also cited our response, dated 17 November 2020, agreeing for them to use DP terminology on components that are not in the final dosage form under (b) (4) (MenACWY-<sup>(b) (4)</sup> vaccine).

**Reviewer comment (MB):** *After consultation with OVRR and OCBQ we concurred that GSK could retain their current nomenclature and to consider MenACWY Lyo and the MenB Liquid as Drug Products. Of note, the DP nomenclature for MenACWY and MenB components is also consistent with other similar co-packaged vaccines.*

**CBER Comment 2:**

*In Section 3.2.P.2.3 Manufacturing Process Development Control Strategy -*  
(b) (4)



(b) (4)

**GSK response to CBER Comment 2:**

(b) (4)

**CBER Comment 3:**

*GSK indicated that they used* (b) (4)

**GSK Response to Comment 3:**

(b) (4)



(b) (4)

. GSK considers that, because all the vials are made from the same materials, they have sufficient data to demonstrate compatibility between MenACWY Lyo and the vials from the three different vendors. Further, GSK states that to confirm compatibility the Leachables studies are ongoing and that they will notify us if unexpected results occur.

(b) (4)

*Please see my reviewer comment to comment 4, below, for information regarding additional information requests.*

GSK provided the following requested information in Section 3.2.R *Regional Information*:

- (b) (4)

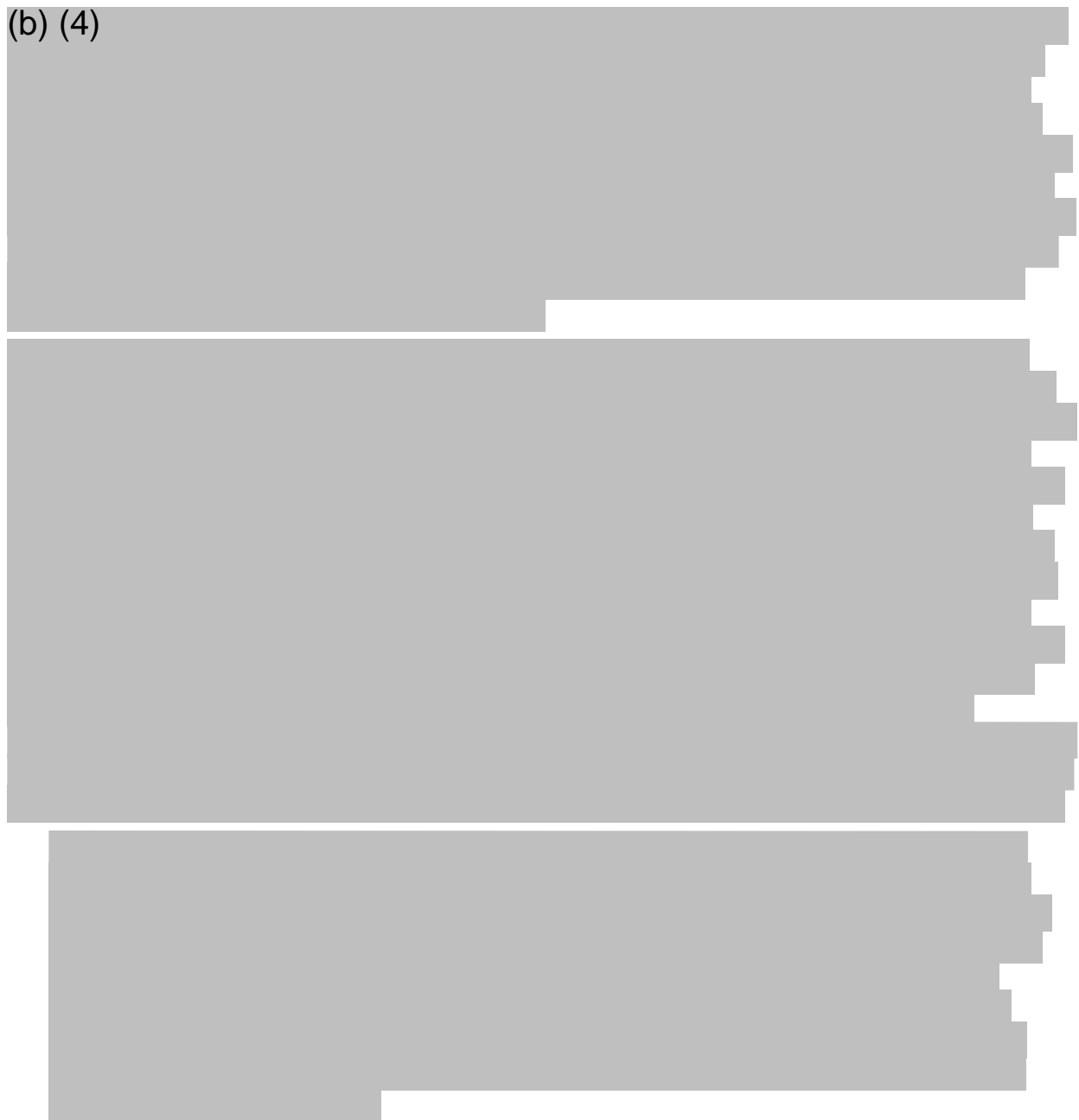
Below I summarize the information contained in each of the document's GSK provided:

(b) (4)

**Reviewer Comment (MB):** GSK previously provided the information contained in this report under Section 3.2.P.2.4 Container Closure System Safety Evaluation, which I reviewed under Section 3.2.P.2.4 Container Closure System of this memo.

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

(b) (4)



**CBER Comment 4:**

*In Section 3.2.P.2.3 Manufacturing Process Development Control Strategy Formulation, Filling and Lyophilization, GSK stated that (b) (4) from the primary container could act as (b) (4). This could impact product quality. Since GSK indicated that they use (b) (4) vials from three different suppliers, it is important that they demonstrate container closure compatibility for each of the vials they intend to use for MenACWY Lyo. We asked them to indicate if they used each of the three vials from the three different suppliers for their long-term stability studies on PPQ/post-PPQ lots. We also asked them to submit stability data for MenACWY Lyo produced with the commercial process, at the proposed end of shelf life, and stored in all container closure*

*systems they intend to use commercially (or the most recent timepoint available if they did not have such data), and asked them to acknowledge that we would determine MenACWY Lyo expiry primarily on the real-time stability data from PPQ and post-PPQ lots, and on whether they have data demonstrating container closure system suitability for the proposed expiry.*

**GSK Response to Comment 4:**

GSK indicated that they (b) (4) in the vial supplied by (b) (4). As described in their responses above, they consider the three vials to be equivalent; they also stated that they use the same vial stopper for all three vials and that they validated the (b) (4) process.

Regarding shelf life, GSK acknowledged our comment and stated that they did not have (b) (4) and that they only had (b) (4). They clarified that they have not yet performed stability data trend analysis that includes the new data they collected.

GSK provided updated stability data for the MenACWY Lyo lots:

- (b) (4)

(b) (4)

**Reviewer comment (MB):** *Despite GSK's claims, we cannot assume container closure equivalency/suitability; the applicant must demonstrate this with data, per 21 CFR 211.94(a) and 21 CFR 600.11(h).*

*The stability results provided in STN 125819/0.13 conform to their respective acceptance criteria for all batches. I do not identify significant trends. I note that GSK (b) (4)*

*We sent additional IRs on 2 August 2024 requesting GSK provide additional supporting documentation to support the use (b) (4) vials (comment 1). We also*

requested GSK include (b) (4) determination as part of their (b) (4) stability monitoring commitment as well as part of their ongoing stability studies (comment 3). GSK responded on 14 August 2024 (**STN 125819/0.22**). As part of their response, GSK notified us that they will not use (b) (4) vials for MenACWY Lyo.

Please refer to my review of amendment 44 (starting on page 187 of this memo) for the updated stability data GSK provided for (b) (4), per their commitment to provide updated stability data (b) (4)

**CBER Comment 5:**

*In Section 3.2.P.3.3 Description of Manufacturing Process and Process Controls -*

(b) (4)

. We therefore asked them to provide data demonstrating that product quality is not impacted (b) (4).

**GSK Response to Comment 5:**

(b) (4)

. To demonstrate no impact to the DP they evaluated the following CQAs:

- (b) (4)

**CBER Comment 6:**

GSK performed the MSD assay robustness study on MenACWY liquid vaccine (MENVEO) instead of MenACWY Lyo, asserting that differences in excipients between

vaccines would not impact the (b) (4) method performance (Section 3.2.P.5.3 Validation of Analytical Procedures (b) (4)). To support GSK's assertion that a separate (b) (4) study for MenACWY Lyo is not necessary, we asked GSK whether they used the same analytical procedure for the MENVEO study as they do for MenACWY Lyo, and to provide data (including (b) (4)) demonstrating that MenACWY Lyo and MENVEO liquid (prepared from the same active ingredients but with different excipients) yield equivalent (b) (4) results.

#### GSK Response to Comment 6:

GSK confirmed that the analytical procedures are identical except for (b) (4) for the MenACWY Lyo product ((b) (4)) as the MenACWY liquid (MENVEO) is already a solution. They also committed to provide the data we requested by the end of July 2024.

GSK provided the (b) (4) STN 125819/0.17 dated 31 July 2024. Furthermore, to demonstrate that different excipients between MENVEO liquid and MenACWY Lyo DP do not impact the (b) (4) outcome, GSK prepared multiple DP samples using the (b) (4) batches:

- (b) (4)

GSK presented the (b) (4) results they obtained for each sample ((b) (4))

**Reviewer comment (MB):** I calculated that the differences in results between samples are within the accepted IP of the method for each parameter (b) (4)

, respectively)). Since the difference in excipients do not significantly impact (b) (4) results and the procedures are identical, I consider GSK's response to be adequate.

#### CBER Comment 7:

In 3.2.P.2.3 Manufacturing Process Development-Analytical Development, GSK indicated they used different (b) (4) instruments for the (b) (4) for MenACWY Lyo Phase (b) (4) and PPQ lots; Alliance for post-PPQ, assay validation, and future commercial batches). They performed a comparability study using (b) (4) representative lots of MenACWY Lyo and concluded that the differences between instruments are negligible. We asked GSK to submit the comparability study report for our evaluation and figures comparing the (b) (4) for the standards, calibration curves, and test samples collected on the (b) (4) instruments. We also asked them to clarify if they use the same

(b) (4) and procedures for data collection, analysis, and to evaluate assay validity and determine system suitability with (b) (4) instruments.

**GSK Response to Comment 7:**

GSK provided document *TR\_2022\_Pre-validation Study on the* (b) (4) in the MenACWY lyo formulation by (b) (4) method in Section 3.2.R. They included a comparability study in which they compared the (b) (4) results (b) (4) they obtained with (b) (4) instruments. They used (b) (4) (b) (4)

**Reviewer comment (MB):** I consider the data GSK provided adequate to support comparing (b) (4) results from Phase (b) (4) PPQ to post-PPQ/commercial batches.

I do not observe meaningful differences between the (b) (4), especially for the standards used to generate the calibration curves from which the (b) (4) are calculated. I note changes in (b) (4) between certain (b) (4) but that could be due to differences between the (b) (4). Nonetheless, the (b) (4) between instruments do not impact calculation of (b) (4)

GSK's response is adequate.

**CBER Comment 8:**

In Section 3.2.P.2.3 Manufacturing Process Development-Analytical development GSK indicated that they intended to only retain (b) (4) with its respective acceptance criterion for commercial batches. However, (b) (4) data in Section 3.2.P.5.3 Validation of Analytical Procedures (b) (4) show that MenACWY Lyo DP subjected to (b) (4) led to changes not only to (b) (4) but also to

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



(b) (4)

**Reviewer comment (MB):** *GSK provided the information and clarification we requested. Therefore, I consider GSK's response to be adequate.*



**Information request letter 25 (dated 10 October 2024) and GSK responses review (amendment 34, dated 24 October 2024)****CBER Comment 1**

*Under IND 14605 amendment 226 GSK requested feedback regarding the information they were planning to include in the BLA to support licensure of MenACWY. In our feedback, we asked you to provide justification for removing the (b) (4) test from the commercial MenACWY Lyo DP testing panel. On 24 July 2024 GSK responded under IND 14605 with data to support that their process controls for producing DP with consistently low (b) (4) content (IND 14605.254). However, we noted that the (b) (4) studies show (b) (4) levels of (b) (4) after 12 months of storage. Due to the (b) (4) content in MenACWY Lyo upon storage and the potential impact on product quality, we asked GSK to include the (b) (4) test in their MenACWY Lyo DP release and stability testing panels with associated acceptance criteria.*

**GSK response to Comment 1:**

GSK included the (b) (4) test in the release and stability monitoring of MenACWY Lyo final container batches as we requested.

To support that the (b) (4) level in the DP would not present a concern, GSK provided the (b) (4) levels of the Phase (b) (4) DP (b) (4) at (b) (4) months (b) (4) compared to the (b) (4) they measured at (b) (4) months of DP storage, see review of amendment 36 directly above). GSK also provided the (b) (4) test results for Phase (b) (4) batches (b) (4), which do not show (b) (4) over time and thus supports that no, or negligible, protein aggregation occurred during storage.

**Reviewer comment (MB):** *The reason for the apparent (b) (4) during storage it is not clear. Nonetheless, the CCS for Phase (b) (4) and PPQ batches, despite being similar, are supplied by (b) (4) respectively). Although the data GSK provided support the use of the (b) (4) vials, the adequacy of the (b) (4) vial for long-term MenACWY Lyo is still being evaluated. Therefore, MenACWY Lyo DP expiry will be set depending on the data GSK will provide in mid-November. Nonetheless, I consider GSK's response to be adequate since they complied with our request.*

To reflect the inclusion of the (b) (4) test as part of MenACWY Lyo DP release and testing panels GSK updated the following documents:

- 3.2.P.2.3 Control Strategy – Formulation, Filling & Lyophilization\_MenACWY Lyo
- 3.2.P.2.3 Analytical Development\_MenACWY Lyo
- 3.2.P.3.5 Process Performance Qualification – Formulation, Filling and Lyophilization\_MenACWY Lyo
- 3.2.P.5.1 Specification(s)\_MenACWY Lyo
- 3.2.P.5.2 Analytical Procedures Overview\_MenACWY Lyo

- 3.2.P.5.3 *Validation of Analytical Procedures – Overview\_MenACWY Lyo*
- 3.2.P.5.4 *Batch Analyses – PPQ Lots\_MenACWY Lyo*
- 3.2.P.5.6 *Justification of Specification(s) – Overview\_MenACWY Lyo*
- 3.2.P.8.2 *Stability Monitoring Commercial Lots\_MenACWY Lyo*
- 3.2.P.8.3 *Stability Analytical Procedures\_MenACWY Lyo.*

**Reviewer comment (MB):** *The changes GSK introduced to these documents adequately reflect the inclusion of the (b) (4) test for MenACWY Lyo DP testing.*

**CBER Comments 2 and 3:** Please see the MenABCWY section of this IR on page 253 of this memo.

**CBER Comment 4:**

*GSK directly copied section 3.2.S.S.1.3 General Properties from the MENVEO BLA. This section was therefore not accurate as it did not include MENVEO as a US-licensed vaccine that uses the CRM197 used for PENMENVY. We asked them to revise this section, as well as any other sections that discuss CRM197's use in other vaccines, to include MENVEO.*

**GSK response to Comment 4:**

GSK acknowledged our comment and corrected the mistake under Section 3.2.S.1.3, *General Properties* for CRM197. *GSK's response is adequate.*

**CBER Comment 5:**

*In Section 3.2.S.4.4 Batch Analyses-Overview for MenC GSK presented different manufacturing dates for the same batch numbers (e.g., MenC batch (b) (4) lists both (b) (4) and batch (b) (4) lists (b) (4)). We asked GSK to explain why the same batches have different production dates and to correct the documentation as needed.*

**GSK response to Comment 5:**

GSK clarified that the different dates reflect those for different process steps or different validation activity for the same batch. To avoid confusion, GSK now includes (in Section 3.2.S.4.4 *Batch Analyses – Overview*) only the final batch manufacturing date (e.g., for batch 0111 the manufacturing date is 7 July 2017). *GSK's response is adequate.*

**Amendment 38 dated 8 November 2024**

GSK submitted this amendment to provide documentation to support qualification of new reference standards, or shelf-life extension of already-qualified reference standards.

**Reviewer comment (MB):** *I provide my review of the updated documentation below. For my review of the comparability protocols, please refer to my review of the documentation that pertains to MenACWY Lyo DP under Section 3.2.R Regional Information of this memorandum.*

GSK introduced the following changes:

- (b) (4)

[REDACTED]

**Reviewer comment (MB):** *I consider the qualified reference standard fit for its intended use.*

- (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]



### 3.2.P DRUG PRODUCT - MenB Liquid Drug Product (*Reviewed by MH unless noted*)

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

The meningococcal B component (referred to herein as MenB Liquid) is a suspension for injection containing the recombinant protein antigens (rp287-953, rp936-741 and rp961c) derived from *N. meningitidis* serogroup B strains and OMV, also, purified from *N. meningitidis* serogroup B. GSK adsorbs the DS to aluminum hydroxide.

The MenB Liquid component is an opalescent, white-colored suspension in a PFS presentation. The PFS is a 1.25 mL Luer lock syringe (Type (b) (4) glass barrel) with (b) (4) rubber tip cap and bromobutyl Type (b) (4) rubber plunger stopper.

MenB Liquid composition per dose (0.5 mL) is:

a) Active Substances:

- rp287-953 50 mcg
- rp936-741 50 mcg
- rp961c 50 mcg
- OMV 25 mcg

b) Excipients:

- Sucrose (b) (4)
- Sodium Chloride 3.125 mg
- Histidine 0.776 mg
- Aluminum Hydroxide 1.5 mg
- Water for injection Up to (b) (4)

#### 3.2.P.2 Pharmaceutical Development

##### 3.2.P.2.1 Components of the Drug Product

MenB Liquid composition is identical to BEXSERO DP (STN 125546/0, approved on 23 January 2015).

##### 3.2.P.2.1.1 Drug Substance

- rp287-953: Recombinant *N. meningitidis* serogroup B NHBA fusion protein.
- rp961c: recombinant *N. meningitidis* serogroup B NadA.
- rp936-741: recombinant *N. meningitidis* serogroup B fHBP fusion protein.
- OMV: OMV from *N. meningitidis*, serogroup B strain NZ98/254, measured as total amount of protein containing PorA P1.4.

##### 3.2.P.2.1.2 Excipients

- Aluminum Hydroxide [Al(OH)<sub>3</sub>]: Adsorbent concentration is (b) (4) to achieve (b) (4) of all antigens. This concentration corresponds to 0.5 mg/dose of elemental aluminum, which is within the allowable dose of aluminum for


human vaccines (upper allowable limit of aluminum adsorbent for injection is 1.25 mg elemental aluminum as per WHO guidance).

- Histidine: A (b) (4) to adjust (b) (4) of the DP, assuring antigen adsorption and product stability.
- Sodium Chloride: A (b) (4) commonly used in parenteral preparations.
- Sucrose: A (b) (4) used to obtain an (b) (4) preparation.
- Water for Injection.

### **3.2.P.2.2 Drug Product**

#### **3.2.P.2.2.1 Formulation Development**

(b) (4)



#### **3.2.P.2.2.2 Overages**

There are no overages. This section does not apply for MenB Liquid.

#### **3.2.P.2.2.3 Physicochemical and Biological Properties**

The MenB Liquid component is a preservative-free, sterile, opalescent liquid (white suspension) for injection.



### 3.2.P.2.3 Manufacturing Process Development

The start of development of the MenABCWY vaccine coincided with BEXSERO Phase 3 clinical development and progressed after licensure of BEXSERO. Thus, GSK has leveraged the knowledge gained with the commercial BEXSERO vaccine to evolve the MenB Liquid manufacturing process. In Table 1 of Section 3.2.P.2.3, GSK provides an overview of those process development. There GSK describes the lots, final DP composition, formulation facility, formulation scale, filling facility, filling line, target fill volume, and PFS for the lots used for during Phases 1 to 3, GMP development, and PPQ, post-PPQ, and commercial manufacturing.

#### BEXSERO pre-Licensure modifications

At the Phase 1/2 stage of MenABCWY development, GSK referred to the (b) (4)

(STN 125546/0). They customized the section 3.2.P.2.3 *Manufacturing Process Development BEXSERO Pre-Licensure Development (from Phase 3 to Commercial)* from BEXSERO to introduce editorial edits, remove irrelevant information, and add the process nomenclature applied to MenB Liquid.


#### BEXSERO post-licensure modifications

After BEXSERO licensure, GSK introduced the following changes in manufacturing process:

- (b) (4)


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

(b) (4)



### 3.2.P.2.4 Container Closure System

GSK customized this section to remove obsolete information related to previously used syringes for BEXSERO (STN 125546/963, approved on 24 February 2023). GSK states that the data presented in this section were generated using BEXSERO vaccine but are fully applicable to MenB Liquid as well, due to the equivalence of the syringe and the product composition. The only difference between both products is the (b) (4)



The (b) (4) syringe composition includes:

- 1.25-mL syringe barrel with a Luer Lock closure system, a large-cut flange, and a (b) (4) rubber tip cap (b) (4) formulation). (b) (4) are the syringe barrel suppliers;
- (b) (4) formulation plunger stopper; and
- A plunger rod.

GSK assessed the suitability of the CCS by testing the following parameters (all reviewed under STN 125546/963, approved on 24 February 2023):

- 1) **Comparability:** GSK included QC release, long-term stability, and accelerated stability testing on qualification lots filled in the syringe. They analyzed (b) (4) BEXSERO qualification lots using the (b) (4) syringe from (b) (4). The company stated that syringes produced by both manufacturers are identical as both companies use the same plunger stopper (manufactured by (b) (4)).  
The manufacturing process of the glass material, which is made of inert borosilicate glass, type (b) (4) used by both providers is not identical.
- 2) **Safety:** In their assessment of safety, GSK demonstrated that the syringe is composed of materials that are considered safe for use with the dosage form and the route of administration intended. Assessment of safety included:
  - Physico-chemical properties
  - Biocompatibility
  - Extractables: For the (b) (4) rubber tip cap, GSK provides the conditions tested in Table 1 of Section 3.2.P.2.4 *Container Closure System* and the analytical methods in Table 2. For the (b) (4) plunger stopper, GSK provides the conditions tested in Table 4 and the analytical methods in Table 6. They also performed a toxicological assessment to identify compounds to be targeted in the leachable studies.
  - Leachables: GSK performed the study on the (b) (4) BEXSERO qualification lots. They provide the target compounds and the analytical methods in Table 8 and the results from the (b) (4)-month time point.
- 3) **Protection:** An opaque secondary packaging provides protection from light. GSK included a container closure integrity test in the long-term stability plan of the (b) (4) BEXSERO qualification lots filled in the (b) (4), with testing timepoints at both (b) (4). The company performed a shipping simulation study to demonstrate that the syringe container closure integrity is not impacted by a sequence of tests simulating the environmental physical hazards encountered during international shipments. After the shipping simulation, they performed a syringe functionality test. This study was performed on (b) (4) different PFS batches from both (b) (4).
- 4) **Quality control of syringe constituents:** GSK tested (b) (4) batches of syringe barrels from (b) (4) batches of plunger stoppers and (b) (4) batches of plunger rods. Results are shown in Tables 16 to 19 of Section 3.2.P.2.4 *Container Closure System*.

**Reviewer comment (MH):** A detailed review of the above information can be found in the CMC memo for STN 125546/963.

### 3.2.P.2.5 Microbiological Attributes

The MenB Liquid is a sterile, preservative-free DP component. GSK takes the following precautions during its preparation to ensure the sterility of the final product:

- Manufactures the DS according to CGMP in controlled environmental conditions to minimize (b) (4) and to assure sterility. GSK monitors the areas for environmental air conditions and clean or sterilize the equipment according to validated methods. Prior to (b) (4), GSK (b) (4) the DS (b) (4) and performs (b) (4) testing.
- Manufactures MenB Liquid according to GMP in controlled environmental conditions to minimize risk from external contamination and assure sterility of the final product.
- Prepares (b) (4) under contamination-controlled conditions using (b) (4) WFI. The (b) (4) containers.
- Formulation occurs in a controlled environment. GSK performs (b) (4) in-process tests before the (b) (4) step. MenB Liquid DP is transported under controlled temperature conditions from the (b) (4) area to the (b) (4) storage room, where it is stored in temperature-controlled conditions until aseptically filling into unit dose syringes.

### 3.2.P.2.6 Compatibility

GSK demonstrated the compatibility of the MenB Liquid component with the container closure components in Section 3.2.P.2.4 *Container Closure System* and through stability studies described in Section 3.2.P.8.3 *Stability Data*.

#### Overall Reviewer's Assessment of Section 3.2.P.2:

MenB Liquid is identical to BEXSERO except for the (b) (4). Thus, GSK leveraged the knowledge gained from the commercial BEXSERO vaccine to manufacture MenB Liquid. During my review, I referred to the approved BEXSERO manufacturing supplements that impacted on MenB Liquid. GSK set a new (b) (4) of MenB Liquid at the (b) (4). I did not identify any deficiencies.

### 3.2.P.3 Manufacture

#### 3.2.P.3.1 Manufacturer(s)

Table 24 lists the facilities involved in the manufacture, testing and warehousing of commercial MenB Liquid component (3.2.P.3.1 *Manufacturer(s)* Table 1):

**Table 24: Manufacturers–MenB Liquid.**

Site Name/Address	Responsibility
GlaxoSmithKline Vaccines S.r.l. Bellaria-Rosia 53018 Sociville (SI) Italy	Formulation and filling, visual inspection, quality control and stability testing, and warehousing
(b) (4) GlaxoSmithKline Vaccines (b) (4)	Warehousing Operations
(b) (4)	Warehousing Operations
(b) (4)	Warehousing Operations

**3.2.P.3.2 Batch Formula**

Batch formula (amount per mL):

- Recombinant *N. meningitidis* protein 287-953 (b) (4) mcg)
- Recombinant *N. meningitidis* protein 961c (b) (4) mcg)
- Recombinant *N. meningitidis* protein 936-741 (b) (4) mcg)
- OMV (b) (4)
- Al(OH)<sub>3</sub> (b) (4)
- NaCl (b) (4)
- Sucrose (b) (4)
- Histidine (b) (4)
- WFI To (b) (4)

The final formulation batch size is from (b) (4)

The nominal maximum filling batch size is (b) (4)

There is no manufacturing overage.

**Overall Reviewer's Assessment of Sections 3.2.P.3.1 and 3.2.P.3.2:**














This section is identical to BEXSERO (STN 125546/259, approved on 8 January 2018). The information is acceptable.

### 3.2.P.3.3 Description of Manufacturing Process

GSK customized the section 3.2.P.3.3 *Overview* to add the process nomenclature (STN 125546/992, approved on 8 June 2023) and change the cross-references to refer to MenB Liquid 3.2.P.3.3 sections. Figure 2 describes the steps in the formulation process and related process control parameters.

The manufacturing process for MenB liquid DP consists of (b) (4) steps:

(b) (4)



**Overall Reviewer's Assessment of Section 3.2.P.3.3:**

The processes are identical to those approved for BEXSERO (STN 125546) at the time of this submission, except for the changes mentioned above. I find the information provided acceptable.

**3.2.P.3.4 Controls of Critical Steps and Intermediates**

This section is identical to BEXSERO. In 2023, GSK updated the IPC tests and re-classified the process parameters for the manufacturing of BEXSERO DP (STN 125546/992, approved on 8 June 2023). GSK classifies the IPCs applied during the manufacturing process as “In-process quality decision (QD) tests” to demonstrate that the process is controlled. Table 1 of Section 3.2.P.3.4 *Control of Critical Steps In-process Quality Decision tests – Specifications and Analytical Procedures* lists the QD tests.

During the formulation step, GSK takes (b) (4) at the following process stages:

- (b) (4)

**Container closure integrity test (CCIT):** The operator (b) (4)

GSK validated this method on BEXSERO PFS, which is the same container used for MenB liquid (3.2.P.3.4 *Controls of Critical*



*steps In-Process Quality Decision tests - Validation of Analytical Procedures – CCIT* and file Validation Report VA-0000373572 in section 3.2.R).

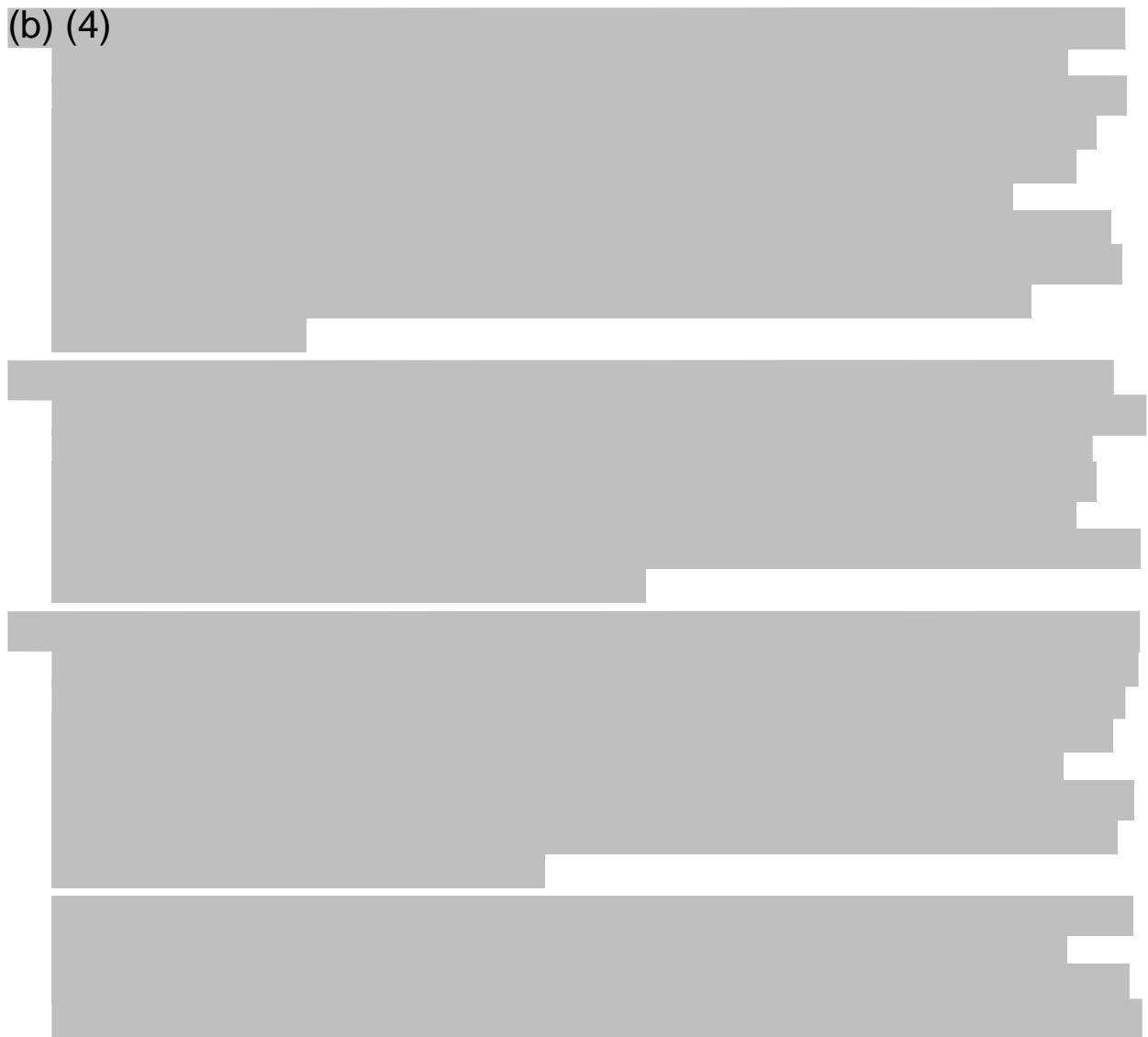
**Overall Reviewer's Assessment of Section 3.2.P.3.4:**

This section is identical to BEXSERO (STN 125546/992, approved on 8 June 2023). I agree with the controls that GSK implemented.

**3.2.P.3.5 Process Validation and/or Evaluation**

Due to the similarity between BEXSERO commercial vaccine and MenB Liquid, several of the validation and evaluation studies performed on BEXSERO commercial vaccine apply to MenB Liquid manufacturing process development and process consistency (STN 125546/259, approved 8 January 2018). Here is a list of the validation studies performed:

(b) (4)





**Overall Reviewer's Assessment of Section 3.2.P.3.5:**

GSK provided data to support the validation of (b) (4) manufacturing processes. Several of the validation and evaluation studies performed on BEXSERO commercial vaccine apply to MenB Liquid manufacturing process development and process consistency (STN 125546/259, approved 8 January 2018). The (b) (4) (b) (4) used in BEXSERO process to (b) (4) (b) (4) for MenB liquid) only requires modification to the (b) (4) (b) (4) program parameters ((b) (4) (b) (4) and not to the existing equipment employed in BEXSERO/MenB Liquid manufacture. GSK provided a PPQ study to support the consistency of (b) (4) (b) (4). Their comparability assessment showed that (b) (4) (b) (4) the dose volume (0.5 mL). As part of GSK's CPV program and data trend analysis, they commit to continue monitoring the (b) (4) (b) (4) attribute and once a minimum number of MenB Liquid commercial batches are available, they will calculate consistency (b) (4) (b) (4). I find the information and justifications provided acceptable.

**3.2.P.4 Control of Excipients****Control of Excipients: Sodium Chloride, Histidine, Sucrose, and Water for Injection (WFI)**

The sections for these excipients are identical to the one in BEXSERO (STN 125546/0, approved on 23 January 2015). All assays are (b) (4) (b) (4). Please refer to the CMC memo for STN 125546/0 for a detailed review.

**Control of Excipients: Aluminum hydroxide****3.2.P.4.1 Specifications**

GSK amended this section in STN 125546/119 to include editorial updates and removed tests not required by (b) (4) (b) (4) (approved on 26 August 2016).

Aluminum hydroxide ((b) (4) (b) (4)) meets with specifications listed in the current (b) (4) (b) (4) listed in Table 1 of Section 3.2.P.4.1 *Specifications – Aluminum hydroxide*.

GSK performs the following (b) (4) (b) (4) specification assays on aluminum hydroxide: (b) (4) (b) (4)

GSK performs the following (b) (4) (b) (4) release assays:

(b) (4)

### **3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures**

GSK customized this section from BEXSERO, which they updated in STN 125546/119, approved on 26 August 2016. Please refer to the associated CMC memo for review of the validations.

### **3.2.P.4.4 Justification of Specifications**

Aluminum hydroxide (b) (4) complies with specifications listed in the current (b) (4) "Aluminum Hydroxide (b) (4)". GSK provides the certificate of analysis of this excipient (CoA) in Section 3.2.R.

### **3.2.P.4.5 Excipients of Human or Animal Origin**

There are no excipients of human or animal origin in the manufacture of BEXSERO and MenB Liquid vaccines.

### **3.2.P.4.6 Novel Excipient**

There are no novel excipients in the manufacture of BEXSERO and MenB Liquid vaccines.

#### **Overall Reviewer's Assessment of Section 3.2.P.4:**

All excipients, their specifications, and validation methods are identical to BEXSERO. I found them adequate to be used to formulate MenB Liquid.

### **3.2.P.5 Control of Drug Product**

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

Since the approval of BEXSERO (STN 125546/0), GSK has updated these sections as follows (see also Table 2 of Section 3.2.P.5.6 *Justification of Specifications Overview*):

**Table 28: Changes to MenB DP Release Specifications since BEXSERO licensure.**

STN	Change Requested	Approval Date
125546/786	(b) (4)	15 July 2021
125546/786		15 July 2021
125546/882		15 March 2022

Table 29 shows the release specifications for MenB Liquid (b) (4), and Table 30 includes the release specifications for MenB Liquid final product (final pack) (adapted from Table 1, 3.2.P.5.1 *Specifications*). Justifications for specifications were reviewed under STN 125546.

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

**Table 30. Release Specifications–MenB Liquid DP (Final Container).**

Test Parameter (Attribute)	Analytical Procedure	Final Acceptance Criteria
Immunochemical Identity (rp961c)	(b) (4)	(b) (4)
Immunochemical Identity (rp936-741)		
Immunochemical Identity (rp287-953)		
Immunochemical Identity (OMV)		
Volume		
Aluminum Hydroxide (b) (4)		
Aluminum hydroxide (b) (4)		Conforms
Appearance	(b) (4)	Opalescent liquid with white suspension
(b) (4)		(b) (4)
(b) (4)		
Endotoxin		
Sterility		No growth

Test Parameter (Attribute)	Analytical Procedure	Final Acceptance Criteria
Visible particles	Visual inspection	Conforms (Absence of foreign particles)
Potency: rp961c	(b) (4)	(b) (4)
Potency: rp936-741		
Potency: rp287-953		
Potency: OMV		
Pyrogen		
(b) (4)		

RP, relative potency; (b) (4)

GSK performs an additional release test for the MenB Liquid final pack to distinguish the packaged product from any other product (except for BEXSERO), according to Title 21 of Code of Federal Regulations (CFR). In this "Identity" test, GSK performs a (b) (4), and the acceptance criterion is (b) (4) (Table 2, 3.2.P.5.1 *Specifications*, and 3.2.P.5.6 *Justification of Specification(s) Identity on Packed Product*).

As discussed earlier in this module, the only difference between the MenB Liquid and BEXSERO is a (b) (4). There is no sufficiently sensitive analytical method available to discriminate this (b) (4) between this two DPs. Thus, under 21 CFR 610.9 "Equivalent Method and Processes," the Company utilizes robust manufacturing procedures and process controls to discriminate between the BEXSERO DP and the MenB Liquid DP PFS and to ensure the two products remain separate. In Figure 1 of Section 3.2.P.5.6 *Justification of Specification(s) Identity on Packed Product*, GSK provides a schematic description of process steps from filling (Rosia site) to packaging (Rosia and (b) (4) sites). Before sending the unlabeled (b) (4) to the warehouse, they include a "Visual inspection step" at Rosia. As part of this process, (b) (4)

that contains the following main information:

- Product name
- Batch number
- Process order
- Barcode
- Relevant SAP code of the product
- Storage temperature

At the end of the labeling step, the operators check the CCU label and record it in the relevant batch record. Depending on the batch size, they distribute labeled (b) (4) from a (b) (4) batch across one or more pallets (Handling Units (HUs)). They label each pallet of material with a unique HU number and a barcode that is tracked within the SAP system. The main HU label information appearing in SAP is:

- Product name
- Quantity
- Description
- Units
- Batch number
- Relevant SAP code of the product
- Storage temperature

Table 1 of Section 3.2.P.5.6 *Justification of Specification(s) Identity on Packed Product* describes all the GMP procedures and controls that are performed at each step occurring between filling and labeling/packaging to avoid product mix up. GSK samples PFS for routine QC release testing at MenB Liquid final container level during the “Visual Inspection step.” In special circumstances (such as for investigational purposes), GSK (b) (4). This activity only occurs in dedicated areas and using strict manufacturing procedures.

In cases where GSK needs to (b) (4), this process may only occur at the (b) (4) to avoid product mix ups (Figure 2, 3.2.P.5.6 *Justification of Specification(s) Identity on Packed Product*).

**Reviewer comment (MH):** In IND 14605.203 GSK requested a partial exemption from 21 CFR 610.14 requirements that they distinguish MenB Liquid DP from BEXSERO, with additional information provided under IND 14605.205 per our request. As there is no mechanism for partial exemptions specified in 21 CFR 610.14, we informed GSK that they could submit a proposal under the Equivalent Methods and Processes regulation (21 CFR 610.9) to utilize manufacturing process controls to discriminate between MenB Liquid PFS and BEXSERO PFS and requested additional information, including reasons why they may (b) (4) a MenB Liquid PFS batch. GSK provided this information under IND 14605.217, which the CMC reviewer found acceptable. Please see associated communications and review memos for the IND amendments.

**Overall Reviewer’s Assessment of Sections 3.2.P.5.1 and 3.2.P.5.6:**

I consider the information provided adequate. The release specifications for MenB Liquid are identical to those approved for BEXSERO. Additionally, GSK has an identity test for MenB Liquid final pack that can specifically distinguish the packaged product from any other product (except for BEXSERO). They implemented multiple process controls and labelling steps to track the final products and avoid mix ups between MenB Liquid and BEXSERO in PFS, per our feedback under IND 14605. I agree that those controls are adequate for this purpose.





1. **Identify the subject and the verb.** The subject is "The committee" and the verb is "has decided".

**LL:** As all (b) (4) validation results met the pre-established acceptance criteria and demonstrated that the (b) (4) is precise, accurate, specific, linear, and robust over the tested range, I consider the assay suitable for relative potency determination of MenB Liquid DP.

Table 1 of Section 3.2.P.5.4 *Batch Analyses Overview* provides information for all the batches used for clinical development, stability, and process changes, whereas Table 2 describes BEXSERO commercial vaccine lots considered relevant for the development of MenB Liquid. The lots used for the manufacturing process development, analytical

development, and process validation of BEXSERO that are relevant for MenB Liquid development due to their similarity are described in section 3.2.P.2.2.1 *Formulation Development MenB Liquid*.

- Nonclinical: (b) (4). All MenB Liquid batches met all the acceptance criteria in place at the manufacturing time.
- Clinical: All batches met all the acceptance criteria.
  - Phase (b) (4)
  - Phase (b) (4)
  - Phase (b) (4)
- PPQ: (b) (4). This batch met all the acceptance criteria.
- Post-PPQ: (b) (4). This batch met all the acceptance criteria.

GSK modified and updated tests, specifications, and release criteria over the investigation of this vaccine. In October 2012, after (b) (4) lot release, GSK changed the specifications and analytical procedures for pyrogens, endotoxin, and immunogenicity, and introduced the (b) (4). They used this lot for clinical validation of the specifications and to retest the parameters according to the new specifications and methods. Later, at the release time of (b) (4) batch (Phase 3), GSK reported the (b) (4) as (b) (4). GSK tightened the acceptance criterion of RP by (b) (4) assay for rp287-953 for commercial lots (from RP (b) (4) RP (RP = (b) (4) result for the PPQ lot complies with the updated acceptance criterion for commercial lots.

**Table 32. BEXSERO Lots used to Support MenB Liquid Development.**

BEXSERO STN (Corresponding 3.2.P.5.4 Document in STN 125819)	Purpose	Batches	Approval Date
(b) (4)			

BEXSERO STN (Corresponding 3.2.P.5.4 Document in STN 125819)	Purpose	Batches	Approval Date
(b) (4)			

### 3.2.P.5.5 Characterization of Impurities

GSK customized this section from STN 125546/0 to improve clarity and add reference to the (b) (4) risk assessment. GSK controls for impurities in the individual DS, as it is difficult to perform a detailed analysis of the DP after the formulation step. They perform (b) (4) tests on MenB Liquid as part of their release specifications, which support product sterility and control for LPS, which could affect reactogenicity. As shown in the (b) (4) risk assessment, there is no risk to find (b) (4) in the DS and DP (3.2.R (b) (4) *Risk Assessment\_MenB Liquid*).

#### Overall Reviewer's Assessment of Sections 3.2.P.5.4 and 3.2.P.5.5:

All MenB Liquid DP batches met all the acceptance criteria set at their respective release times. I agree with GSK's approach to characterize impurities.

### 3.2.P.6 Reference Standards or Materials

Identity by (b) (4) (3.2.P.6 *Reference Standards or Materials Identity by* (b) (4))

- rp287-953: (b) (4) (Exp July 2027), 3.2.S.5 *Reference Standards and Materials rp287-953*
- rp936-741: (b) (4) (Exp June 2024), 3.2.S.5 *Reference Standards and Materials rp936-741*
- rp961c: (b) (4) (Exp July 2024), 3.2.S.5 *Reference Standards and Materials rp961c*
- OMV: (b) (4) (Exp May 2026), 3.2.S.5 *Reference Standards and Materials OMV*

**Reviewer comment (MH):** In **125819/0.27**, GSK replaced batch (b) (4) with (b) (4) as the rp936-741 reference standard for the determination of Identity by (b) (4), Purity by (b) (4), Purity by (b) (4) and Purity and Content by (b) (4). Similarly, they replaced batch (b) (4) with batch (b) (4) as rp961c reference standard for the determination of Identity by (b) (4), Purity by (b) (4), Purity by (b) (4) and Purity and Content by (b) (4) (125819/0.27 and STN 125546/1214, approved on 8 November 2024). However, they did not update this section. Thus, we sent IR# 26 requesting them to update this section (**28 October 2024**). In **STN 125819/0.37**, GSK provided an updated section 3.2.P.6

*Reference Standards or Materials Identity by (b) (4), to include the current reference standards:*

- rp936-741: (b) (4) (Exp November 2029), 3.2.S.5 *Reference Standards and Materials rp936-741*
- rp961c: (b) (4) (Exp April 2030), 3.2.S.5 *Reference Standards and Materials rp961c*

(b) (4) (3.2.P.6 *Reference Standards or Materials* (b) (4))

- rp936-741: (b) (4) (Exp Feb 2026)
- rp287-953: (b) (4) (Exp Jun 2026)
- rp961c: (b) (4) (Exp Apr 2026)
- OMV: (b) (4) (Exp Jul 2025)

The (b) (4) batch is the approved positive control for this assay (STN 125546/786, approved on 15 July 2021). They used these new rp reference standards for the testing of MenB Liquid post-PPQ and will continue to do so for subsequent commercial lots. GSK qualified the new standards according to the approved master comparability protocol VA-0000476363-PQ&PV in section 3.2.R *Regional Information* (STN 125546/786, approved on 15 July 2021). According to the master comparability protocol, GSK estimates (b) (4) of the candidate batches. They then perform (b) (4)

The acceptance criterion is (b) (4). GSK then verifies the equivalence of the (b) (4) obtained using the reference standards in use and the new reference standards in (b) (4) different analytical sessions. Within each analytical session, the (b) (4) of those (b) (4) must be between (b) (4) otherwise the analysis must be repeated.

GSK provided qualification report VA-0000650415 *rp Reference Standards for* (b) (4) in section 3.2.R *Regional Information*. For rp287-953, GSK initially failed to calculate the (b) (4) (Table 5). They measured lower (b) (4). Thus, they postulated it was due to a possible error in the step of (b) (4), probably due to an insufficient (b) (4). GSK prepared new (b) (4) for rp287-953 and repeated the assay for the (b) (4) rps (Table 7). All subsequent sessions were valid and met the acceptance criteria. Then, they performed the bridging study (Table 10). The (b) (4) from the bridging study (1.0) met the acceptance criterion.

All batches can be used as reference standards for (b) (4)

**Pyrogens by** (b) (4) (3.2.P.6 *Reference Standards or Materials Pyrogen by* (b) (4))

The BEXSERO batch (b) (4) (Exp March 2025) is the positive control for this assay (STN 125546/896, approved on 13 September 2022). The provided qualification report (VA-0000537642 – *Qualification Report* – (b) (4)) is the same one that GSK included for BEXSERO.

(b) (4) (3.2.P.6 Reference Standards or Materials Potency by (b) (4); reviewed by MH and LL)

The BEXSERO batch (b) (4) (Exp March 2025) is the positive control for this assay (STN 125546/991, approved on 1 June 2023). The provided qualification report (VA-0000539449) is the same one that GSK included for BEXSERO.

GSK provides a list of the comparability protocols to validate new reference standards. The protocol files are in Section 3.2.R. We approved those protocols for BEXSERO (STN 125546/229, approved on 16 March 2021; STN 125546/800, approved on 25 August 2021; STN 125546/804, approved on 24 August 2021; STN 125546/896, approved on 13 September 2022, and STN 125546/991, approved on 1 June 2023).

**Reviewer comment (MH and LL):** On 12 June 2024, GSK sent us an e-mail due to an increasing trend over time of (b) (4) results for the BEXSERO/MenB Liquid recombinant protein (rp) antigen rp287-953 when using batch (b) (4) as standard. The use of this batch impacts the (b) (4) test executed at release and stability testing since July 2023. On 30 August 2024 (IND 14605.256), GSK provided a list of the lots and tests affected using batch (b) (4) (Table 1, section 1.11.1 Quality Information Amendment MenABCWY IND 14605). The investigational batches affected are:

(b) (4) : This is a PPQ batch to support the filling process of MenB liquid filled in (b) (4) line with a (b) (4) and using (b) (4) as primary container. It affected stability data at (b) (4) -month timepoints.

(b) (4) : This is a post-PPQ batch to support manufacturing changes as part of life-cycle management of BEXSERO implemented since the production of the MenABCWY PPQ lots and reflected in the MenABCWY commercial production at launch. It affected stability data at (b) (4) -month timepoints.

(b) (4) : These are BEXSERO batches to support using (b) (4) as primary container. It affected stability data at the (b) (4) month timepoints.

(b) (4) : This is a Phase 3 clinical batch. It affected stability data at the (b) (4) month timepoint.

Due to a trend for (b) (4) potency of reference standard (RS) lot (b) (4) for the rp287-953 antigen, GSK qualified a new RS lot (b) (4) according to the Master Qualification Protocol VA-000232500 V3.0 (approved under STN 125546/991 on 01 June 2023). As this new RS will be used for the stability testing of MenB liquid post-PPQ at the (b) (4) -month timepoint, GSK provided qualification report (VQD-RPT-300189) in **STN 125819/0.40** (parallel submission to STN 125546/1205). To select candidate lots, (b) (4) analysts initially tested (b) (4) BEXSERO lots (b) (4) over (b) (4) analytical sessions for each antigen using the lot (b) (4) as the RS and calculated the GM(RP) for each antigen in each of (b) (4) candidate lots. GSK selected (b) (4) lots (b) (4) for the qualification phase testing because, among all the (b) (4) candidate lots, these (b) (4) lots had GM(RP) nearest to (b) (4) for all the antigens. In the qualification phase, (b) (4) analysts tested

(b) (4) in (b) (4) independent analytical sessions for each antigen. GSK calculated the correction factor (CF) of each antigen based on the (b) (4) RP values obtained from the screening phase and the qualification phase. Although both (b) (4) lots met the qualification criteria, GSK selected (b) (4) as the new RS as the distance of (b) (4) is closer to (b) (4) than the distance of (b) (4). GSK previously submitted the same qualification report to BEXSERO (STN125546/1205) as product correspondence on 30 August 2024. They submitted their responses to our IRs (conveyed on 20 September 2024 under STN 125546/1205) regarding this product correspondence on 15 November 2024 (STN 125546/1205.3). Please refer to review documents and memos for STN 125546/1205 for additional information.

Compared to the previous RS lots, the new RS lot (b) (4) has an obvious (b) (4) in CFs for antigens rp287-953 and OMV. GSK stated that the (b) (4) in CF for rp287-953 antigen is attributed to the (b) (4) in rp287-953 potency over time for former RS lot (b) (4). The (b) (4) CF for OMV could be mainly due to the slight (b) (4) in PorA amount as a consequence of changes implemented to the preparation and composition of the (b) (4) (approved under STN 125546/560 on 20 December 2019) as well as the age of RS lot (b) (4). Therefore, to ensure the final container lots will comply with the clinically justified end-of-shelf-life specification limit (RP (b) (4)), GSK has set up In-house Release Limits (IRL) for assessing the RP of rp287-953 and OMV antigens in BEXSERO/MenB Liquid lots. GSK stated that they determined the IRL after considering the estimated potency decay over the (b) (4)-month expiry period and the bias due to inaccurate CF determination at the (b) (4) RS qualification. They evaluated the estimated potency decay over time by mathematically modelling the rp287-953 and OMV potency data obtained from (b) (4) BEXSERO lots of different ages and determined the bias of the RS lot (b) (4) as the ratio between the CFs calculated at the time of (b) (4) qualification and the new CFs computed using a new statistical approach. GSK is planning to request a Type D meeting to discuss this new statistical approach in detail with us in the context of BEXSERO.

The formula used to set the IRLs of rp287-953 and OMV is:

(b) (4)

Based on this formula, GSK determined the IRL for OMV as RP (b) (4) for rp287-953. They will assess the potency results of rp287-953 and OMV antigens obtained with RS lot (b) (4) against (b) (4) IRLs. In the meantime, for the (b) (4) testing of MenB Liquid final container lots, GSK will continue to use the CFs determined at the time of RS lot (b) (4) qualification.

**Overall Reviewer's Assessment of Section 3.2.P.6:**

The batches listed here can be employed as reference standards for their corresponding assays. The information provided is acceptable.

### 3.2.P.7 Container Closure System

GSK customized this section from BEXSERO to remove information related to the BEXSERO secondary packaging not applicable to MenB Liquid; otherwise, is identical (STN 125546/961, approved on 26 April 2023 and STN 125546/963, approved on 24 February 2023). GSK included the same E&L studies that they previously submitted for BEXSERO (STN 125546/963, approved on 24 February 2023). The E&L studies *Extractable Study Report* (b) (4), *plunger stopper* (b) (4), *Extractable Study Report* (b) (4), *tip cap* (b) (4), and *Leachable Study Report* (b) (4) \_BEXSERO\_ (b) (4) are in Section 3.2.R.

#### Overall Reviewer's Assessment of Section 3.2.P.7:

I agree that the 1.25-mL Luer Lock (b) (4) can be used to store MenB Liquid, as was approved for BEXSERO.

### 3.2.P.8 Stability

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

GSK provided a summary of the three ongoing stability studies (Table 1, Section 3.2.P.8.1 *Stability Summary and Conclusion*). In each study, they placed (b) (4) batch on long-term stability studies. At the time of submission, they had long-term stability data up to 42 months at 2–8°C (3.2.P.8.3 *Stability Data – Long-Term – Phase 3 Clinical* (b) (4) \_MenB Liquid). They also provided up to (b) (4) months long-term data to support the filling process of MenB liquid filled in (b) (4) line with a (b) (4) and using (b) (4) as primary container (3.2.P.8.3 *Stability Data – Long-Term – PPQ* (b) (4) \_MenB Liquid). The third study is for a post-PPQ (b) (4) produced with (b) (4) produced with manufacturing changes as part of lifecycle management of BEXSERO that impact the MenABCWY commercial production (3.2.P.8.3 *Stability Data – Long-Term – Post-PPQ* (b) (4) \_MenB Liquid). They provided up to 6 months of long-term stability data and they will continue this study up to (b) (4) months. All the data collected by GSK for the three studies are within the acceptance criteria and they did not report any OOS results.

In **STN 125819/0.44**, GSK provided updated stability data. They completed the long-term stability study at 2–8°C (3.2.P.8.3 *Stability Data – Long-Term – Phase 3 Clinical Lot\_MenB Liquid*). All the data are within the acceptance criteria, and they did not report any OOS results. Therefore, they confirmed that MenB Liquid's increased target fill volume compared to BEXSERO does not impact the stability profile, that all the attributes are well within the acceptance criteria, and it is stable up to 48 months.

GSK also updated the PPQ Lot MenB Liquid long-term study to include the 24-month timepoint. All the data are within the acceptance criteria, and they did not report any OOS results.

**Reviewer comment (MH):** The data collected support the MenB Liquid (b) (4) and use of (b) (4) at 2–8°C up to 24 months. Relative potency by (b) (4) for rp936-741 follows a (b) (4) trend. This parameter should be closely

monitored because if this tendency continues it would be OOS before the (b) (4)-month timepoint.

GSK updated the post-PPQ (b) (4) MenB Liquid long-term study to include the 9-, 12-, and 18-month timepoints. They reported that initially Relative Potency by (b) (4) results at 9 months for rp936-741 and rp287-953 were invalid due to an incorrect setting of the respective acceptance criterion for the (b) (4) reference standard batches. They reported valid results after recalculating them using the correct settings. All the data collected in this study are within the acceptance criteria, and GSK did not report any OOS results.

GSK also updated the BEXSERO Liquid long-term (b) (4) to include the 24- (b) (4) month timepoints. All the data collected by GSK in this study are within the acceptance criteria, and they did not report any OOS results. This demonstrates the stability of BEXSERO final container (b) (4) upon (b) (4) months storage at +2°C to +8°C.

In Table 2 of Section 3.2.P.8.1 *Stability Summary and Conclusion*, GSK provided the concluded and ongoing BEXSERO stability studies that are relevant to MenB liquid DP.

**Table 33: BEXSERO Stability Studies to Support MenB Liquid DP.**

STN (associated Sections 3.2.P.8.3 in STN 125819)	Study Summary	Approval Date
125546/563 ( <i>Stability Data – Long-Term – (b) (4) Formulation Process (b) (4) _MenB Liquid; Stability Data – Accelerated (b) (4) Formulation Process (b) (4) _MenB Liquid</i> )	Stability studies for manufacturing process at (b) (4) Formulation Process (b) (4) months and (b) (4) months for long-term and accelerated, respectively)	2 November 2020
125546/575 ( <i>Stability Data – Long-Term – (b) (4) _MenB Liquid</i> )	Stability study to support the introduction of (b) (4) months)	27 January 2020
125546/786 ( <i>Stability Data – Long-Term - (b) (4) _MenB Liquid; Stability Data – Accelerated - (b) (4) _MenB Liquid</i> )	Stability studies to support the introduction of the (b) (4) (48 months and (b) (4) months for long-term and accelerated, respectively)	15 July 2021
STN 125546/758 and 125546/882 ( <i>Stability Data Long term (b) (4) (b) (4) ; Stability Data Accelerated (b) (4)</i> )	Stability studies to support the shelf-life extension of BEXSERO vaccine from (b) (4) months to (b) (4) months (b) (4) months and (b) (4) months for long-term and accelerated, respectively)	30 March 2021 15 March 2022
125546/961 ( <i>Stability Data – Long-Term – (b) (4) _MenB Liquid; Stability Data Accelerated (b) (4)</i> )	Stability studies to support the use of the 1.25 mL Luer Lock syringe with (b) (4) rubber tip cap and (b) (4) plunger stopper (b) (4) months long-term)	26 April 2023

The GSK proposes a shelf life of 48 months for MenB Liquid, when stored at the recommended temperature of 2–8°C, as already approved for the commercial



BEXSERO vaccine. They base this shelf life on the stability data available for the BEXSERO commercial vaccine, which they consider fully representative of MenB Liquid stability, and the stability data they collected up to now on MenB Liquid (described above).

### 3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment

GSK proposes to complete the ongoing stability studies:

- PPQ (b) (4) long-term study for (b) (4) months (3.2.P.8.2 *Post-Approval Stability Protocol and Stability Commitment PPQ Lot*).
- Post-PPQ (b) (4) MenB liquid long-term stability study up to (b) (4) months (3.2.P.8.2 *Post-Approval Stability Protocol and Stability Commitment Post-PPQ (b) (4)*). The objective of this study is to support a (b) (4)-month shelf life for MenB Liquid final container at 2–8°C.
- (b) (4) MenB Liquid long-term stability study up to (b) (4) months (3.2.P.8.2 *Post-Approval Stability Protocol and Stability Commitment (b) (4)*).

For MenB Liquid commercial lots, GSK will follow at least (b) (4) for commercial stability (3.2.P.8.2 *Post-Approval Stability Protocol and Stability Commitment Stability Monitoring of Commercial Lots*). MenB Liquid final container will be placed (b) (4) and stored for (b) (4) months at 2–8°C. They plan to test samples (b) (4) months) with the following tests:

- Appearance by visual inspection: Opalescent liquid with white suspension
- (b) (4)
- Visible particles by visual inspection: Absence of foreign particles
- Endotoxin content by (b) (4) method: (b) (4)
- Sterility by (b) (4): No growth (0, 36, 48 and (b) (4) months)
- Relative Potency by (b) (4) (for each antigen): (b) (4)
- Container closure integrity by (b) (4) test: (b) (4)
- (b) (4) (for each antigen): (b) (4)

#### Overall Reviewer's Assessment of Section 3.2.P.8:

I agree with the shelf-life of 48 months for MenB Liquid, when stored at the recommended temperature of 2–8°C. I also concur with GSK's commitment to complete all the ongoing stability studies and to monitor (b) (4) for commercial stability using the proposed timepoints and tests. In **STN 125819/0.73** (10 February 2025) GSK clarified that expiry dating would be based on the formulation date as the date of manufacture.

## Information Request Letters for MenB Liquid Review

For each Information Request, I have provided a brief synopsis of each comment followed by GSK's responses and my review.

### Information Request Letter dated 21 June 2024 and GSK responses review (amendments 14 and 28 dated 10 July 2024 and 27 September 2024)

#### CBER comment 1:

*GSK initially developed and validated the (b) (4) assay for 4CMenB in the Analytical Research and Development (ARD) Laboratory, and then transferred it to the Quality Control (QC) laboratory, where routine testing is performed (Section 3.2.P.5.3 Validation of Analytical Procedures (b) (4)). While they evaluated assay precision and compared the reproducibility between QC and ARD laboratories, GSK did not assess the accuracy of (b) (4) in the QC Laboratory; therefore, we asked them to evaluate the accuracy of (b) (4) using incurred samples with relative potency covering the ranges for the assays.*

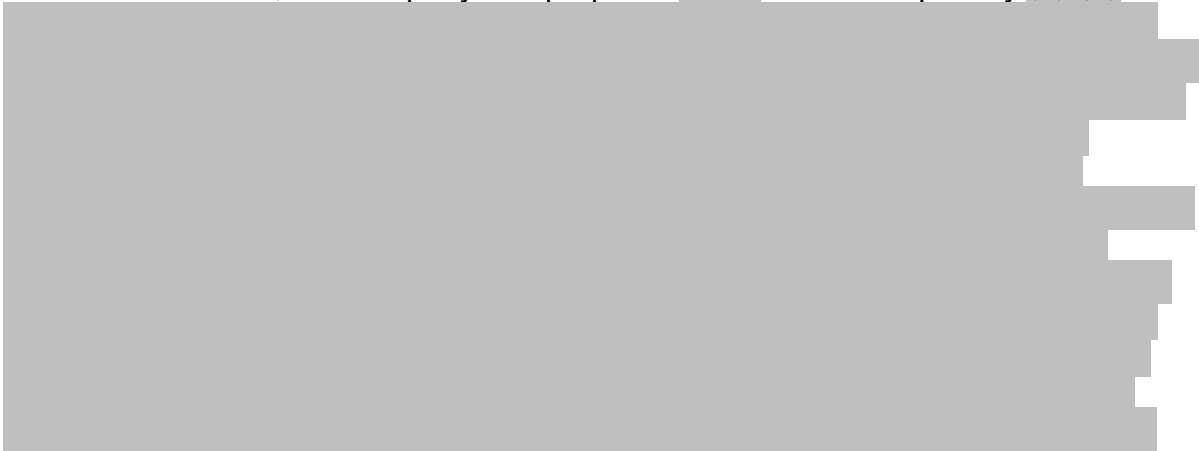
**Initial response (Amendment 14, 10 July 2024):** The company acknowledged our comment and clarified that they submitted their method transfer plan in STN 125546/758, approved on 30 March 2021. In line with guideline ICH A2 *Validation of Analytical Procedures*, the company initially evaluated the data of representative samples (RP = (b) (4)) and performed a (b) (4) equivalence analysis. The (b) (4) results showed that the RP values obtained from the QC lab were equivalent to the values obtained from the ARD lab, as the data met the pre-defined acceptance criterion that the CI of the difference between the mean of the natural-log-transformed RP values between two labs should be within (b) (4). Thus, the accuracy, repeatability, and intermediate precision were demonstrated in the QC receiving lab using the representative samples. The company included this equivalence result in section 5.12 *Reproducibility* of an updated version of the validation report.

In addition, the company also compared the data generated on (b) (4) different BEXSERO lots during their investigation of a failure for out of specification in 2018, in which BEXSERO lots (b) (4) were tested in parallel at both labs for comparability purposes. The data showed that, for antigens rp287-953 and rp961c, the RP results generated in both labs at the target (RP = (b) (4)) and lower end of range (RP = (b) (4)) were comparable.

To demonstrate the accuracy at the lower and upper boundaries of the analytical range for the four MenB antigens in QC lab, the company indicated that they would prepare mock samples representing different target potencies (i.e., (b) (4)) and test them at the QC lab. The company will submit the outcome of experiment by the end of September 2024 (see "second response," immediately below).

**Second response (Amendment 28, 27 September 2024):** GSK submitted the data they described under their response in STN 125819/0.14 (described directly above)

to confirm the relative accuracy across the entire range of the (b) (4) assay in the QC lab. In the new test, the company first prepared (b) (4) mock samples by (b) (4)



**Reviewer comment (LL):** Together, the results submitted under amendments 14 and 28 confirmed the accuracy of the (b) (4) method in the QC lab across the validated RP range of (b) (4). The company's response is adequate.

**CBER comment 2:**

In their (b) (4) analytical procedure (b) (4) and Master Qualification Protocol file VA-0000232500-3.0, GSK indicated that they reported the system and sample suitability criteria for (b) (4) in document (b) (4); however, they did not provide this document. We asked them to provide a summary of system and sample suitability criteria and to add them to the (b) (4) Analytical Procedure.

**Response (Amendment 14, 10 July 2024):** The company acknowledged our comment and provided an overview of system suitability criteria for the (b) (4) assay in Table 1 and overview of sample suitability criteria for the (b) (4) assay in Table 2 of Section 1.11.1 *Quality Information Amendment IR-11*. In addition, the company also reported these criteria in (b) (4) and LSOP-APP9000079544.

**Reviewer comment (LL):** The company's response's is adequate.

**CBER comment 3:**

GSK's additional experiment for the stability of (b) (4) for antigens rp936-741 and OMV only confirmed the (b) (4) was stable up to (b) (4) days ("Validation of Analytical Procedures (b) (4)" document), but GSK that the (b) (4) for antigens rp936-741 and OMV were robust for (b) (4) days. We asked them to correct the discrepancy.

**Response (Amendment 14, 10 July 2024):** The company acknowledged our comment and corrected the typographical errors in Figures 7, 8, 10, and 12, as well as the errors in Table 15. In addition, they clarified the stability of (b) (4) for rp936-741 and OMV antigens was calculated starting from (b) (4) date to (b) (4) date. Therefore, the correct information for the stability of (b) (4) is (b) (4) days for rp936-741 and OMV. Thus, the information provided in Table 13 and Table 23 of the initial report is correct. The company revised section 3.2.P.5.3 *Validation of*

*Analytical Procedures* (b) (4) *MenB Liquid* to include the corrected figures and table listed above, as well as corrected text to align with the data included with Table 16 and Table 25 pertaining to rp936-741 and OMV (b) (4) stability.

**Reviewer comment (LL):** *The company's response is acceptable.*

### **3.2.P DRUG PRODUCT-MenABCWY (Reviewed by MB unless noted)**

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

GSK packages the MenABCWY reconstituted vaccine (RV) as a combination product comprising the MenACWY Lyo in 3-mL (b) (4) Type (b) (4) glass vial containers sealed with 13-mm bulk stoppers and secured with flip-off caps and MenB Liquid in pre-filled (≥0.5 mL) syringes (1.25 mL Type (b) (4) glass syringe barrel with Luer Lock closure, (b) (4) rubber tip cap and a Bromobutyl Type (b) (4) rubber plunger stopper). The end user generates the RV by reconstituting the MenACWY Lyo vial with the entire contents of the MenB Liquid PFS to form an opalescent liquid with white suspension. This procedure ensures that 0.5 mL can be administered per dose. The active ingredients and excipients are listed under sections 3.2.P.2.1.1 and 3.2.P.2.1.2 below.

#### **3.2.P.2 Pharmaceutical Development**

##### **3.2.P.2.1 Components of the Drug Product**

###### **3.2.P.2.1.1 Drug Substance**

The RV is composed (per syringe) of the active ingredients: 10 mcg of MenA-CRM, 5 mcg each of MenC-, MenW-, and MenY-CRM, 50 mcg each of MenB proteins rp287-953 (NHBA), rp936-741 (fHBp), and rp961c (NadA), and 25 mcg of OMV.

###### **3.2.P.2.1.2 Excipients**

The vaccine contains the following excipients: 22.5 mg sucrose, 3.125 mg NaCl, 0.776 mg histidine, 0.7 mg potassium phosphate salts (this amount varies because in addition to the potassium phosphate in MenACWY Lyo, (b) (4) ), 1.5 mg of aluminum hydroxide, and (b) (4) of WFI.

##### **3.2.P.2.2 Drug Product**

###### **3.2.P.2.2.1 Formulation Development**

GSK provides an overview of the development studies they performed on MenABCWY RV, including a compatibility study to demonstrate that there are no physicochemical or biological incompatibilities between MenACWY Lyo and MenB vaccine components.

###### **3.2.P.2.2.2 Overages**

GSK applies a (b) (4) for MenACWY Lyo but not to MenB Liquid; however, to ensure full MenACWY Lyo reconstitution GSK fills the PFS with (b) (4) compared to BEXSERO.

###### **3.2.P.2.2.3 Physicochemical and Biological Properties**

Please refer to the separate DP component sections, above.

### 3.2.P.2.3 Manufacturing Process Development Analytical development

GSK divided the tests they performed throughout product development into three categories: Quality Release (QR), Characterization (C), and Surveillance (S, which includes assays that report on parameters whose link to product quality is unknown or for which GSK still needed to define their acceptance criteria). However, after Phase 3 (PPQ/Commercial) GSK re-categorized the assays to QR or C only.

In Section 3.2.P.2.3 *Manufacturing Process Development Analytical Development*, GSK presents a summary of all the analytical changes they introduced during MenABCWY RV development. These include:

**Endotoxin:** GSK used Endotoxin (by (b) (4) for Phase (b) (4) DP release but removed it for Phase (b) (4). In response to IND 14605.237 we requested that they provide Endotoxin test results for PPQ batches (see communication dated 21 January 2024). GSK re-introduced the Endotoxin assay for PPQ and post-PPQ/commercial lots. However, because they test for Endotoxin in the individual components (i.e., MenACWY Lyo DP and MenB Liquid DP) they do not include it as a MenABCWY release test; however, the applicant does include it in the stability testing panel.

**Reviewer comment (MB):** *Because GSK performed studies to demonstrate compatibility between MenACWY Lyo and MenB, I consider it redundant to perform Endotoxin release testing for the individual MenACWY Lyo and MenB Liquid DP and for the RV; therefore, removing Endotoxin testing from the MenABCWY RV release panel but retaining it for stability monitoring of PPQ/post-PPQ lots is adequate. However, based on the information GSK provides in Section 3.2.P.2.3 Manufacturing Process Development Analytical Development, they do not intend to retain Endotoxin testing for RV stability monitoring of commercial lots. GSK does retain the (b) (4)*

*which can detect changes in Pyrogenicity during RV storage.*

*Nonetheless, on 10 October 2024 (comment 2) we requested that GSK include the endotoxin test for routine release testing of the RV vaccine. On 24 October 2024 GSK submitted STN 125819/0.34 in which they complied with our request. Please refer to the review section beginning on page 254 for additional information.*

**Pyrogenicity:** GSK performed the (b) (4)

**Appearance:** GSK introduced the assay for Phase (b) (4) lots. They have retained the test and have not introduced any changes to the assay or its acceptance criterion.

**Extractable volume:** GSK introduced the assay for Phase (b) (4) lots. For Phase (b) (4) and Phase (b) (4) lots, however, it was a (b) (4) assay, and for PPQ/commercial, GSK measures the RV extractable volume by (b) (4) without any change to the acceptance criterion.

(b) (4)

### 3.2.P.2.4 Container Closure System

The container closure system for MenABCWY RV is the PFS described under 3.2.P.2.4 *Container Closure System* for the MenB Liquid DP. However, the vaccine is supplied in two container closure systems, one containing MenACWY Lyo DP (CCS described under 3.2.P.2.4 *Container Closure System* for the MenACWY Lyo DP) and one containing the MenB Liquid DP (described under 3.2.P.2.4 *Container Closure System* for the MenB Liquid DP). The combined, reconstituted MenABCWY is within the PFS and must be used immediately.

### 3.2.P.2.5 Microbiological Attributes

To preserve the sterility of the final reconstituted vaccine, GSK indicates that the RV should be administered immediately. While GSK validated a (b) (4) hold time at 2–8°C through in-use stability data (see section 3.2.P.8.3 below), they revised their application to remove the hold time based on CBER feedback (see **STN 125819/0.53**).

### 3.2.P.2.6 Compatibility

To support compatibility between the MenACWY Lyo and MenB components GSK performed three studies:

1. MenACWY Lyo and MenB Liquid physicochemical comparability (b) (4) mixing.
2. Similar to the first study but with MenACWY Lyo and MenB Liquid (b) (4) of their proposed shelf lives.
3. In-use stability using (b) (4) material and measuring (b) (4) and (b) (4) after (b) (4) (or (b) (4) for one attribute; see below).

**Physicochemical comparability:** To determine if critical quality attributes of the combined product are impacted by combining the separated components, GSK evaluated:

- Antigen integrity/potency (for MenA-CRM GSK determined (b) (4) by (b) (4), and for MenB components by (b) (4))

- Endotoxin
- Identity

The strategy GSK followed is equivalent to the one they reported in IND 14605.237 (23 August 2023; please refer to the CMC memorandum for amendment 237, dated 29 January 2024 and the information request we communicated to GSK on the same date) for which GSK supported comparability through statistical analysis of the respective assay results. Briefly, I describe and review below the results for each of the studies GSK performed.

GSK used a combination of commercial BEXSERO lots ((b) (4)) and Phase (b) (4) MenACWY Lyo lots (b) (4) as well as a development lot (b) (4) (prior to manufacturing Phase (b) (4) lots). For all the batch permutations GSK performed please see Section 3.2.P.2.6 *Compatibility*.

- (b) (4) assay: GSK combined MenACWY Lyo and MenB Liquid to generate the RV. They performed the (b) (4) assay immediately after combining and repeated the assay after RV storage at 2–8 °C for (b) (4). The MenA (b) (4) remains below the LOQ of (b) (4) right after (b) (4) and after (b) (4) of storage. GSK concludes that they demonstrated compatibility between the components in terms of MenA (b) (4).

**Reviewer comment (MB):** GSK did not provide data to demonstrate that the (b) (4) assay is adequate for its intended use in the presence of MenB active ingredients and excipients. For instance, (b) (4) could potentially be adsorbed on  $\text{AlOH}_3$  precluding detection. Therefore, I consider that these results are inconclusive. However, please refer to my evaluation of (b) (4) assay results for the EoSL study GSK performed, which I do consider supportive of compatibility between MenB and MenACWY Lyo components.

- Identity for MenB antigens: GSK evaluated identity by (b) (4) analysis using antigen-specific antibodies. They compared the (b) (4) for the RV with those for the reference standard (a BEXSERO batch) to qualitatively determine if the (b) (4) they observed are equivalent to those of reference standards and if the antigens are intact (i.e., they do not observe additional (b) (4) compared to those for the standard). All the results they report conform to the acceptance criterion.
- (b) (4)



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

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

- Endotoxin: GSK measured endotoxin content for MenB (b) (4) MenACWY Lyo reconstitution at time (b) (4) and after (b) (4) of storage at 2–8°C. They used the BEXSERO Endotoxin acceptance criterion of (b) (4) and the average Endotoxin results for BEXSERO clinical lots (b) (4) to define that a change in the release result of (b) (4) could be of clinical relevance (i.e., (b) (4) (b) (4) which is half the difference between the Endotoxin acceptance

criterion and the mean Endotoxin result, in (b) (4). Thus, if the difference in Endotoxin results between MenB and MenABCWY is within (b) (4) the results are considered equivalent. The difference in Endotoxin content between vaccines fell within the (b) (4) range, supporting no change in potential reactogenicity of MenB components in MenABCWY.

*EoSL study:* To support compatibility of the DP components at the end of their respective proposed shelf lives, GSK utilized Phase (b) (4) lots (b) (4) (MenACWY Lyo) and MenB Liquid (b) (4), stored for (b) (4) months and (b) (4) months, respectively. They evaluated potency of the antigens (b) (4) reconstitution using the following methods:

- (b) (4)

GSK validated these assays in the context of the RV vaccine to support their use for the intended purpose. Consequently, in Section 3.2.R *Regional Information*, GSK provided the validation reports for (b) (4) (VA-0000718861-PQ&PV), (b) (4) for MenW and MenY (VA-0000712949-PQ&PV), (b) (4) for MenC (VA-0000716065-PQ&PV), and for (b) (4) (VA-0000594936-PQ&PV).

- MenA change in potency evaluation: GSK validated a new method for MenA-CRM (b) (4) determination because the method in place for MenACWY Lyo is not suitable for use with MenABCWY RV. The (b) (4) assay uses a (b) (4)

(b) (4)



(b) (4)

**Reviewer comment (LL):** On 21 August 2024, together with the CMC statistical reviewer, we sent an Information Request asking GSK to provide details on the experimental design and the raw data in an analyzable format (comment 1). GSK responded in **STN 125819/0.26** (3 September 2024). Please see page 253 of this memo for additional information.

*In-use stability study:*

**Reviewer comment (MB):** In response to IRs we conveyed related to the updated stability data GSK provided in STN 125819/0.44, GSK removed their (b) (4) in-use period (see **STN 125819/0.53**). Regardless, for completeness, we have retained our review of the in-use stability study in this memorandum.

GSK performed an in-use stability study on MenACWY Lyo and MenB Liquid samples stored at 2–8°C for a period of (b) (4) months (MenACWY Lyo) or (b) (4) months (MenB Liquid). They then evaluated RV quality using the potency tests described above for the EoSL evaluation, as well as evaluating (b) (4) MenB antigens (b) (4), and appearance for the EoSL samples (b) (4) reconstitution and (b) (4) (for all except MenCWY CS) and up to (b) (4) (for MenCWY CS determination, due to assay time constraints) (b) (4) reconstitution and storage at 2–8°C. For quantitative results, GSK used the same statistical analysis and acceptance criteria as they used for their compatibility evaluation, except for (b) (4), for which they used the release acceptance criterion (b) (4). However, instead of comparing the results they obtained for the samples (b) (4) reconstitution they evaluated the results for samples (b) (4) reconstitution and (b) (4) the reconstituted samples.

- (b) (4)

**Reviewer comment (MB):** The applicant did not include (b) (4) in their compatibility, EoSL, and in-use studies to support no change in pyrogenicity in the EoSL product and during the in-use storage period. GSK includes Endotoxin and Pyrogenicity as stability assays to support no change in the MenACWY Lyo and MenB Liquid product safety profiles during storage (Section 3.2.P.8.3 Stability Data Stability Analytical Procedures). Per our Information Request on **10 October 2024** (comment 3), GSK also added Endotoxin testing at release and during (b) (4) stability monitoring (please refer to the Information Request section beginning on page 254). Combined with GSK's revised instructions to use MenABCWY immediately upon reconstitution (see **STN 125819/0.53**), this mitigates any risk of the applicant not performing endotoxin testing in their compatibility studies.

**Overall Reviewer's Assessment of Section 3.2.P.2:**

We consider the data GSK provided within this section supportive of compatibility between MenACWY Lyo and MenB components. However, because GSK's conclusions regarding compatibility of MenACWY Lyo and MenB components were drawn primarily from statistical data evaluation, we consulted OBPV statisticians. Based on data provided in amendment 44, the OBPV statisticians concluded that reconstituting MenACWY Lyo with MenB can lead to a potential (b) (4) in MenA-CRM content of up to (b) (4) (with 95 % confidence). Therefore, on 2 December 2024 we requested GSK (b) (4) for MenA-CRM in MenACWY Lyo DP to compensate for the potential (b) (4) MenA-CRM content during the in-use period. However, in their response (**STN 125819/0.53**, dated 10 December 2024) GSK informed us that instead of adjusting (b) (4) acceptance criteria, they removed the (b) (4) in-use recommendation from the BLA. GSK now recommends that the vaccine be used immediately after reconstitution. Therefore, it is no longer necessary for GSK to adjust the MenA-CRM (b) (4) acceptance criteria for MenACWY Lyo and the information provided is adequate.

**3.2.P.3 Manufacture****3.2.P.3.1 Manufacturer(s)**

GSK lists the following facilities related to MenABCWY manufacturing, control, and warehousing activities:

**Table 34. MenABCWY Manufacturers.**

<b>Manufacturer</b>	<b>Activities</b>
GlaxoSmithKline Vaccines S.r.l. (Bellaria-Rosia)	Labelling and packaging for the final product Warehousing operations QC/QA (Identity testing only) and release and stability testing of the final MenABCWY product and the RV
(b) (4) GlaxoSmithKline Vaccines (b) (4)	Labelling and packaging Warehousing operations QC/QA and release of the final MenABCWY product
(b) (4)	Warehousing operations

**3.2.P.3.2 Batch Formula**

Please see Section 3.2.P.3.2 under each of the DP components.

**Overall Reviewer's Assessment of Sections 3.2.P.3.1 and 3.2.P.3.2:**

The information in these sections is acceptable.

### 3.2.P.3.3 Description of Manufacturing Process

Because MenABCWY is obtained through combination of two products supplied in a vial (MenACWY Lyo) and PFS (MenB Liquid) there are no manufacturing activities involved other than labelling, packaging, and related controls.

Vials and PFS are automatically labelled and packaged on a labelling machine. Vial labels are printed with lot number and expiry information and subsequently adhered to the vial and then the labeled vials are placed in a carton. For the PFS, the plunger is screwed on each syringe's stopper, and then the syringe is labeled with a label containing lot number and expiry information and placed in the carton with the vial and a product information leaflet. Each carton is also printed with the lot number and expiry. Finally, the cartons are checked and placed in shipping boxes which are identified, palletized, and stored at 2–8°C.

**Batch Numbering System:** GSK refers to the final product (or final pack) as the Combo Carton that contains the MenACWY Lyo final container (vial) and the MenB (PFS). GSK assigns each Combo Carton a five-digit alphanumeric lot number through a SAP system. Additionally, when GSK places the MenACWY Lyo vial and MenB PFS in the carton, the respective lot numbers are replaced by Combo Carton lot numbers followed by an A (for MenACWY Lyo) and B (for MenB Liquid). The expiry GSK prints on the Combo Carton is the earliest expiry of the two components, however, the vial and the PFS retain their respective expiration dates.

#### Overall Reviewer's Assessment of Sections 3.2.P.3.3:

The information provided is acceptable.

### 3.2.P.3.4 Controls of Critical Steps and Intermediates

As there are no manufacturing activities for MenABCWY DP, GSK did not include this section and thus did not describe any controls above those implemented for each of the two DP components. Please refer to the respective DP sections above.

#### Overall Reviewer's Assessment of Section 3.2.P.3.4:

Not applicable as the applicant did not provide this section in the BLA.

### 3.2.P.3.5 Process Validation and/or Evaluation

GS did not include this section as there are no manufacturing activities for the MenABCWY DP; the only process is labeling and packaging the MenACWY Lyo vial and MenB Liquid PFS into the Combo Carton.

GSK did perform shipping validation studies which they reported under 3.2.A *Facilities and Equipment – Cold Chain*. GSK indicates that product transfer between manufacturing facility buildings and product shipment are temperature controlled and



that product transportation has been qualified (transport qualification is described in 3.2.A Facilities and Equipment-Cold Chain).

**Reviewer comment (MB):** GSK did not include any product-related data for review in the shipping validation studies. I defer to the DMPQ reviewer for evaluation of product shipping validation.

**Overall Reviewer's Assessment of Section 3.2.P.3.5:**

As indicated above, the only process associated with MenABCWY manufacture is packaging of the two DP components into the Combo Carton and associated labeling. Please refer to the respective DP component sections 3.2.P.3.5 for details regarding the process evaluations for MenACWY Lyo and MenB Liquid.

**3.2.P.4 Control of Excipients**

Please refer to the DP component sections, above.

**Overall Reviewer's Assessment of Section 3.2.P.4:**

The MenABCWY DP does not contain any additional excipients beyond those described under MenACWY Lyo and MenB Liquid DP.

**3.2.P.5 Control of Drug Product**

**3.2.P.5.1 Specifications and 3.2.P.5.6 Justification of Specifications**

GSK performs the following tests (with the respective acceptance criterion in parenthesis):

- Appearance (by visual inspection, white opalescent liquid)
- (b) (4)
- Visible particles (by visual inspection, free from visible particles)
- Extractable volume (by (b) (4) 0.5 mL)
- (b) (4)
- Pyrogenicity (b) (4)

In this section I only include the justification for assays with associated quantitative acceptance criteria.

- (b) (4)

- **Pyrogen:** The acceptance criterion was defined to be consistent with BEXSERO since the MenACWY Lyo component does not increase the pyrogenicity of the final product.

**Reviewer comment (MB):** I consider GSK's approach to define the (b) (4) acceptance criterion acceptable as I find it conservative: if pyrogens are introduced to the product through MenACWY Lyo, then it will lead to OOS or out-of-trend pyrogenicity results.

**Overall Reviewer's Assessment of Sections 3.2.P.5.1 and 3.2.P.5.6:**

The information provided is adequate.

**3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures**

Per a meeting between DRMRR, DBSQC, and DBPAP on 28 March 2024, the review of MenABCWY method validation falls under DBSQC purview. Therefore, I only include assay descriptions in this section of the memorandum and defer to DBSQC for review of the associated validation studies.

GSK performs the (b) (4), Visible Particles, Extractable Volume, and (b) (4) assays according to (b) (4).

**Appearance:** GSK evaluates the (b) (4)

**Pyrogenicity:** The assay is based on (b) (4)

**Overall Reviewer's Assessment of Sections 3.2.P.5.2 and 3.2.P.5.3:**

I defer to the DBSQC reviewers for assessment of the MenABCWY analytical procedures.

**3.2.P.5.4 Batch Analyses**

GSK provided batch numbers for MenACWY Lyo, MenB Liquid, and MenABCWY RV used throughout clinical development. Below I only include Phase 3, PPQ, and post-PPQ batches. Please see the respective DP component BLA sections for batch genealogy for Phase 1 and Phase 2 batches.

- (b) (4)



### 3.2.P.5.5 Characterization of Impurities

GSK did not provide this section. However, as the manufacturing process consists of co-packaging already two packaged DP, no additional impurities are introduced during the DP manufacturing process and thus it is not applicable.

**Overall Reviewer's Assessment of Sections 3.2.P.5.4 and 3.2.P.5.5:**

The information GSK provided support adequate release of RV batches. I did not identify any concerning trend on the release data.

### 3.2.P.6 Reference Standards or Materials

**In-house reference standards:** GSK uses a reference standard for the Pyrogenicity assay (by (b) (4)). In this assay GSK uses the same reference standard as for the MenB Liquid, which is a BEXSERO lot.

GSK provided a comparability protocol for qualification of (b) (4) in Section 3.2 *Regional Information-VA-0000166988-4.0*, which I evaluate below under Section 3.2.R.

### 3.2.P.7 Container Closure System

Please see the separate DP sections above for descriptions of the vials (MenACWY Lyo) and PFS (MenB Liquid).

**Overall Reviewer's Assessment of Section 3.2.P.7:**

The container closures for MenABCWY are the same as used for the MenACWY Lyo and MenB Liquid components.

### 3.2.P.8 Stability

As agreed in a communication with GSK (in response to additional feedback requested under IND 14605/226, dated 1 September 2023), GSK will not include MenB Liquid and MenACWY Lyo potency assays in the MenABCWY long term-stability studies since they validated the assays for use in the RV and showed that vaccine potency (even for product at EoSL) conformed to release acceptance criteria.

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

GSK performed stability studies to support:

- the in-use stability for up to (b) (4) after MenACWY Lyo reconstitution with MenB Liquid (in-use stability), and
- that there is no impact to MenABCWY RV after MenACWY Lyo and MenB Liquid storage at different time points.

GSK performed the in-use stability study at the beginning (b) (4) months) and at intermediate storage time-points (b) (4) months) for MenACWY Lyo and MenB Liquid. They state that they will also perform the in-use stability study (b) (4) of MenACWY Lyo and MenB Liquid shelf-lives (EoS, section 3.2.P.8.1 *Stability Summary and Conclusion*). However, as can be seen in Section 3.2.P.8.3 *Stability Data In-Use Study*, GSK used different acceptance criteria for the in-use study at the (b) (4) timepoints; therefore, the results can only to be compared within each study but not between studies.

GSK evaluated (b) (4), Appearance, (b) (4) MenB Antigens. For the in-use stability data at the (b) (4) shelf life, the applicant identified at (b) (4) in (b) (4) (Section 3.2.P.8.3 *Stability Data In-Use Study*), however, they state that they mistakenly stored the samples at (b) (4) instead of under the recommended storage conditions. Therefore, the initial study is not representative of the expected routine sample handling. For the in-use study at (b) (4) time points, GSK decided to amend the stability protocol such they would evaluate results equivalency thorough statistical analysis.

For the (b) (4) time point, because the (b) (4) values remained unaltered and because Appearance is not a quantitative assay, GSK performed statistical evaluation to determine results equivalency at (b) (4) and (b) (4) only for (b) (4) MenB Antigens. In their evaluation they calculated the 90% confidence intervals for the mean difference in results (at (b) (4) and (b) (4)) from each assay and evaluated them vs the respective acceptable equivalence margins (b) (4) for (b) (4) for (b) (4). All the results conformed to the equivalence acceptance criteria, thus supporting results equivalency (3.2.P.8.3 *Stability Data - In Use Study*).

#### **Long-term stability data:**

- Phase 3 lots: 36 months of long-term (stored at 2–8°C) stability data for Phase 3 lots (b) (4) (MenACWY Lyo and MenB Liquid lots stored for up to 36 months, then reconstituted and tested).

For these batches GSK evaluated (b) (4), Appearance, Visible Particles and (b) (4) (for surveillance purposes). All the results conform to the respective acceptance criterion at 36 months. There is an apparent (b) (4) in (b) (4) in 36 months of storage (b) (4) (b) (4) however, because all the batches at release yielded a mean result of (b) (4) of (b) (4) whereas at 36 months the mean result is (b) (4) (with 95% confidence), thus, the results seem to be within assay variability. Nonetheless, there is no acceptance criterion in place for this attribute (Section 3.2.P.8.3 *Stability Data Long-Term Phase 3 Clinical Lots*).

- PPQ lots: Between 12–18 months of long-term stability data: 18 months for (b) (4).

For PPQ lots (b) (4), and (b) (4), GSK evaluated (b) (4) (for surveillance purposes). GSK tested for (b) (4) for release and at (b) (4) months (not (b) (4) months), but they are scheduled for testing at all subsequent time points (24, 26, 48, (b) (4) months).

For PPQ lots (b) (4) GSK also measured (b) (4).

All the results conform to the respective acceptance criteria for the tested period (b) (4) or (b) (4) months, Section 3.2.P.8.3 *Stability Data Long-Term - PPQ Lots*). There is an apparent (b) (4) MenB Antigen during the (b) (4) month storage period. However, there is no acceptance criterion in place for this attribute (Section 3.2.P.8.3 *Stability Data Long – Term PPQ Lots*). A similar (b) (4) trend is observed for batches (b) (4) stored under accelerated (b) (4) or under (b) (4) conditions (b) (4).

- Post-PPQ lot: Up to (b) (4) months of long-term stability data for lot (b) (4)

GSK provided limited stability data for this batch. GSK evaluated (b) (4), (b) (4).

**Reviewer comment (MB):** I cannot evaluate data trending due to the limited data available (release results for (b) (4)

The results provided conform to the respective acceptance criteria.

GSK provided updated stability data for their Phase 3, PPQ, and post-PPQ batches in STN 125819/0.44. GSK concluded the (b) (4) in-use period had no impact on CQAs. However, because GSK drew their conclusions primarily from a statistical data evaluation, we consulted OBPV statisticians. The OBPV statisticians concluded that reconstituting MenACWY Lyo with MenB can lead to a potential (b) (4) in MenA-CRM content of up to (b) (4) (with 95 % confidence, please see my review of beginning on page 256 for details). Therefore, on 2 December 2024 we requested GSK to increase the lower acceptance criteria boundaries for (b) (4) for MenA-CRM in MenACWY Lyo DP to compensate for the potential (b) (4) in MenA-CRM content during the in-use period. GSK responded on 10 December 2024 **STN 125819/0.53**) that they decided to remove the (b) (4) in-use period and instead now recommend that MenABCWY be used immediately after reconstitution.

**Reviewer comment (MB):** Based on their response in STN 125819/0.53, I no longer consider it necessary for GSK to adjust MenA-CRM (b) (4) for MenACWY Lyo DP to ensure there is no (b) (4) in MenA-CRM during the in-use period, as the applicant removed this in-use period in favor of instructing the user to administer immediately.

### 3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment

**Phase 3:** GSK will monitor the batches at (b) (4) and (b) (4) months to conclude the study in which they will test for (b) (4) (for surveillance purposes).

**PPQ and post-PPQ:** GSK will monitor these batches following ICH guidelines for up to (b) (4) months. GSK will test for (b) (4)

**Commercial lots:** Initially, GSK did not consider it necessary to perform long term-stability studies on commercial MenABCWY lots. However, per our **10 October 2024** IR (comment 3), GSK committed to enroll MenABCWY RV on (b) (4) stability monitoring (**STN 125819/0.34**; see review beginning on page 254 of this memo).

GSK commits to perform the in-use stability study on the MenACWY Lyo and MenB Liquid at the EoSL. The in-use study includes assays to assess changes in MenACWY and MenB Liquid potency but does not include assays to monitor safety-related assays (Endotoxin and Pyrogenicity) whereas long-term stability studies do not include potency-related assays but do include safety-related assays.

On 22 January 2025, GSK submitted updated 3.2.P.8.2 *Post-Approval Stability Protocol and Stability Commitment Stability Monitoring of Commercial Lots* to reflect the addition of an (b) (4)-month testing timepoint, reflecting the 18-month MenACWY Lyo shelf life (**STN 125819/0.65**).

#### Overall Reviewer's Assessment of Section 3.2.P.8:


GSK addressed all our concerns with amendments 34, 36, and 53. GSK has adequate stability assays in place to ensure no change in product safety occurs during product storage. The initial compatibility study results GSK provided supported that the Phase 3 MenACWY Lyo and MenB Liquid DP do not exhibit potency changes at the end of shelf life or over the in-use period of (b) (4). However, in amendment 44, dated 14 November 2024, GSK provided updated stability study results which included in-use stability evaluation of PPQ DP batches stored for up to (b) (4) months prior to reconstitution. We observed an apparent (b) (4) in MenA-CRM content during the in-use period. However, it was not clear to us if the (b) (4) is significant. Because GSK's conclusions of no potency impact were derived from statistical analysis, we consulted with OBPV statisticians. OBPV indicated that MenA-CRM content (b) (4) during the in-use period. Based on interaction via Information Request, GSK elected to omit the (b) (4) in-use period after reconstitution and now recommend for the reconstituted vaccine be used immediately (for details please refer to my review of amendment 44). The data GSK provided for this section are adequate.

**Information Request Letters for MenABCWY Review**

For each Information Request, I have provided a brief synopsis of each comment followed by GSK's responses and my review.

**Information Request Letter dated 21 August 2024 and GSK responses review (amendment 26 dated 3 September 2024)**

(b) (4)



**Reviewer comment (LL):** *We discussed these results with the statistical reviewers (29 October 2024) who agreed that the data are acceptable. The company's response is adequate.*





**Amendment 44 review (dated 14 November 2024)**

As a pre-BLA agreement (please refer to IND14605.202 dated 15 September 2022 and our response dated 28 October 2022), GSK committed to support MenABCWY RV expiry by submitting the most up-to-date stability data for Phase 3, PPQ, and post-PPQ of MenB, MenACWY Lyo, and MenABCWY RV.

*MenABCWY RV long-term stability data*

GSK provided the following updated long-term and in-use stability data for MenABCWY RV batches:

- Phase 3: 48 months of long-term stability for batches (b) (4) [REDACTED] GSK will not provide additional stability data on Phase 3 batches as they completed all the studies they planned on these batches (Section 3.2.P.8.2 *Post-Approval Stability Protocol and Stability Commitment Phase 3 Clinical Lots*). All the tested attributes remained invariant during the storage period.

- (b) (4) [REDACTED]



### 3.2.A APPENDICES

#### 3.2.A.1 Facilities and Equipment

We defer to DMPQ for review of this module.

#### 3.2.A.2 Adventitious Agents Safety Evaluation

**MenACWY Lyo (MB):** GSK states that they implemented a rigorous GMP-based materials management program to control material sourcing and qualification. The only raw material GSK uses in the MenACWY Lyo DP manufacturing process (b) (4)

(b) (4) MenA, MenC, MenW, MenY, and CRM production) that is from human or animal-derived materials is (b) (4)

(b) (4) GSK also included the (b) (4) statement, indicating that the (b) (4) are obtained (b) (4) healthy animals, are sourced from (b) (4) and are deemed adequate for human consumption.

Furthermore, because microbial organisms can enter the aseptic manufacturing process through personnel, equipment, facilities, and materials, the applicant has implemented a quality management program to address all potential contamination sources through:

- Appropriate personnel management: Enforcement of the use of personal protective equipment, operator training and by restricting the access to facilities to only healthy individuals.
- Equipment and facilities are designed to limit contamination. The instruments and facilities are qualified with validated cleaning and sterilization methods. Furthermore, the facilities are environmentally monitored to address potential contamination.
- Raw materials are handled and stored such to minimize contamination and are controlled through a management program which controls sourcing, qualification, testing and release.

Because the process itself uses (b) (4), GSK ensures that during the process the (b) (4) (in the case of *N. meningitidis* serogroups, via the introduction of (b) (4).

GSK assesses for bioburden throughout the (b) (4) processes as well as for the DP process, which also controls for DP sterility.

**MenB (MH):** In Table 1, GSK listed the (b) (4) raw materials of animal or human origin used in the manufacture of MenB Liquid (b) (4)

MenB Liquid is a sterile suspension. GSK uses validated facilities and equipment with established cleaning and sterilization methods and appropriate training of personnel. Media components are sterile, and the solutions are generally sterile or filtered to reduce bioburden prior to use. GSK puts in place bioburden and sterility controls at appropriate stages of production.

The company assessed the specific risk of transmitting (b) (4) MenB Liquid. They wrote the (b) (4) Risk according to the requirements of the (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

GSK determined that there is no risk of transmitting (b) (4) through MenB Liquid. Thus, they did not perform specific (b) (4) clearance studies. In addition, GSK determined that there is negligible risk of introducing viral adventitious agents during the MenB Liquid manufacturing process. Like for other products derived from bacterial fermentation, GSK considered that specific virological testing during the manufacturing process is not necessary, and no specific viral clearance studies were carried out.

**Reviewer comment (MH):** *As discussed in the CMC review sections, there are controls and assays in place to ensure the biosafety and sterility of the entire MenB Liquid DP (and the associated DS comprising MenB Liquid) manufacturing process. Based on the information provided, all the raw materials of animal or human origin used in the manufacture of MenB Liquid do not pose a risk of transmitting (b) (4) viruses.*

### Viral Clearance Studies

Not applicable.

#### Overall Reviewer's Assessment of Section 3.2.A.2:

**MB and MH:** We reviewed GSK's evaluation of its control strategy to mitigate risks of endogenous and exogenous adventitious agents. The control strategy is adequate. We did not identify any deficiencies.

### 3.2.A.3 Novel Excipients

Not applicable.

### 3.2.R Regional Information (USA)

In this section GSK includes a 3.2.R *Regional information Overview* document containing all the information that they included in the section arranged in different categories with hypertext links to the respective documents to facilitate their access.

**Reviewer comment (MB and MH):** *Because multiple documents included in this section are essential for review of the CMC-related material of the BLA, we included reviews of that documentation in the pertinent Sections 3.2.S and 3.2.P, above. In addition, GSK submitted many documents located under MENVEO (STN 125300)*

*and BEXSERO (STN 125546), which we have listed for completeness. Thus, below we indicate whether we reviewed the document in this section, reference the memo section where we reviewed the documentation, or list the MENVEO or BEXSERO supplement where it was previously reviewed.*

**i. Certificates of Analysis**

GSK only provided certificates of analysis (CoA) for DS batches that they used to manufacture MenACWY Lyo post-PPQ DP. For MenACWY Lyo DP batches, GSK only provided CoA for PPQ and post-PPQ (also characterization assays CoA as a separate document). However, they also provided DS and DP batch release data for non-clinical, clinical, PPQ, and post-PPQ batches in Section 3.2.S.4.4 *Batch Analysis* and Section 3.2.P.5.4 *Batch Analysis*. Similarly, GSK provided CoA for DS batches that they used to manufacture MenB Liquid post-PPQ DP. They provided the CoA for MenB Liquid PPQ and PPQ DP.

GSK also included CoA for raw materials and excipients they used of the MenACWY Lyo DP and MenB Liquid post-PPQ lots.

**Reviewer comment (MB and MH):** *The information GSK provided is adequate as the test results conformed to the respective acceptance criteria included in the CoAs.*

**ii. Batch Records and Master Batch Records**

**Reviewer comment (MB):** *GSK provided executed batch records in Italian. Therefore, on 31 October 2024 we requested GSK translate the documentation and re-submit for our evaluation. GSK provided the documentation we requested on 14 November 2024 (STN 125819/0.43). I did not identify other deficiencies in the documentation GSK provided.*

**MenACWY Lyo (MB):** GSK provided executed batch records (BR) and master batch records (MBR) for the PPQ and post-PPQ MenACWY Lyo lots and for all DSI and DS batches that they used to manufacture the post-PPQ MenACWY Lyo lot. All MBR were translated from Italian to English. GSK included BR and MBR for different production stages for representative batches for each DSI and DS, and MenACWY Lyo DP.

GSK also included a document providing a list of all the changes they introduced in the MBR documents since they executed BR for PPQ (Section 3.2.R *Regional Information-Overview of Changes Between MBRs Since Process Qualification*). These changes fall into two categories: editorial changes (to improve documentation, i.e., alignment of the summary table with all other MBRs) and for continuous improvement of production without quality impact (i.e., additional control checks during production, such as “inclusion of verification of machine parameters” or “check the information on the final product” to the MBR).

**Reviewer comment (MB):** *The BR and MBR appear complete. I did not identify deficiencies in the documentation GSK provided.*

**MenB Liquid (MH):** GSK provided executed BR and MBR for the PPQ and post-PPQ MenB Liquid lots and for all DS batches that they used to manufacture the post-PPQ MenB Liquid batch. They included the DS BR and MBR for all the manufacturing steps. As the copies of the batch records are either in German or Italian, GSK provided blank translated master versions of the batch records. In response to our 31 October 2024 IR, GSK provided the filling, MVI, and AVI batch records with English translations of handwritten notes (**STN 125819/0.43**, 14 November 2024). In Section 3.2.R *Overview of changes between executed and blank MBRs since process qualification*, GSK described all the changes that they introduced in the MenB Liquid MBRs. The changes are mostly document improvement, for better traceability of the operative instructions, and alignment with the SOP.

**Reviewer comment (MH):** *I did not identify deficiencies in the documentation GSK provided. All batches met all the specifications.*

### iii. Method Validation Package

#### **SOPs, Working Instructions (WIs), validation reports, and other documentation relevant for analytical methods**

All WI/SOP related to DSI and DS testing for use in MenACWY Lyo DP manufacturing are identical to those provided under STN 125300, since these DSI and DS are identical to MENVEO.

**Reviewer comment (MB):** *Because the DSI and DS documents were already reviewed under STN 125300, I do not review or list them here.*

MenACWY Lyo:

**Reviewer comment (MB):** *I reviewed the adequacy of the following analytical procedures performed on MenACWY Lyo DP together with the validation of the respective analytical procedures in 3.2.P.5.3 Validation of Analytical Procedures section of this memo (beginning on page 123):*

- SOPs:

- (b) (4)

[REDACTED]

[REDACTED]

- (b) (4)

MenABCWY:

**Reviewer comment (MB):** I reviewed the adequacy of the following validation reports for the analytical procedures performed on MenABCWY DP under 3.2.P.2.6 Pharmaceutical Development-Compatibility section of this memo (page 235):

- (b) (4)

#### Qualification Reports for reference standards, internal controls, and reagents

MenACWY DSI and DS:

- (b) (4)



- MenC-CRM:

- (b) (4)

GSK qualified the above-listed reference standards/PC/NC according to approved protocols (see “Comparability Protocols,” below).


*MenACWY Lyo:*

- (b) (4)

**Reviewer comment (MB):** GSK qualified all the internal and positive controls described above for use in MenACWY Lyo DP testing, according to the qualification

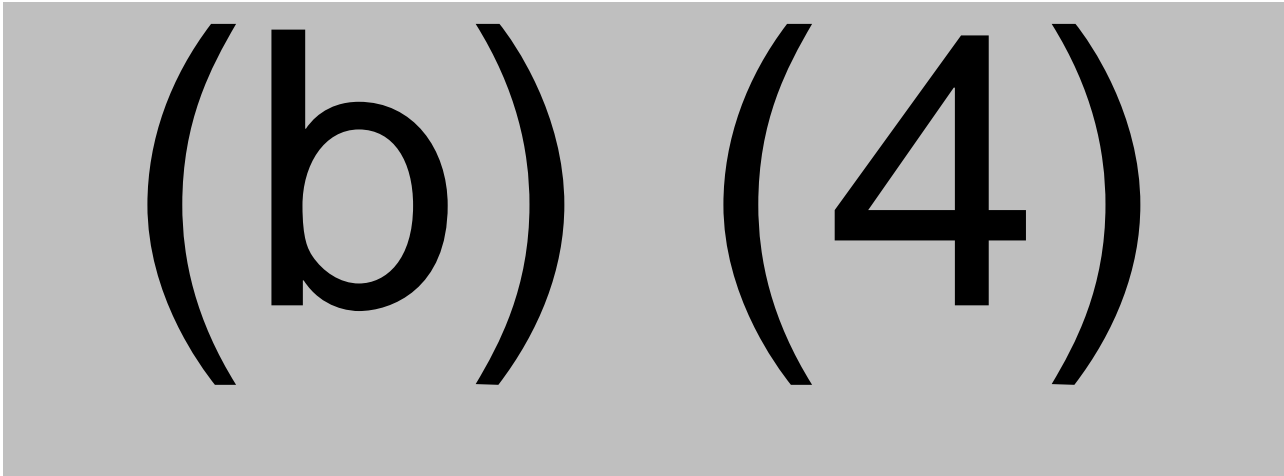
*protocols I evaluated under the “Comparability Protocols” section of this memorandum, below. I did not identify any deficiencies.*

*MenB DS and DP:*

- (b) (4)
- 

**Reviewer comment (MH):** In 3.2.S.4.2 Analytical Procedures, 3.2.S.4.3 Validation of Analytical Procedures, 3.2.S.5 Reference Standards or Materials, I reviewed the SOP, qualification, validation, and verification reports for rp287-953, rp936-741, rp961c, and OMV DS. In 3.2.P.5.2 Analytical Procedures, 3.2.P.5.3 Validation of Analytical Procedures, and 3.2.P.6 Reference Standards or Materials, I reviewed the SOP, qualification, validation, and verification reports for MenB Liquid DP. In the table below, I have listed the included documentation approved previously under BEXSERO.

**Table 35. SOP, qualification, validation, and verification reports approved under BEXSERO.**



(b) (4)

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

(b) (4)

**iv. Combination Products**

We defer this section to the device reviewer.

**Additional documentation GSK provided under Section 3.2.R:**

- (b) (4) Risk Assessment MenACWY Lyo (MB): GSK performed separate (b) (4) risk assessments for MenB DP, MenA-CRM, MenC-CRM, MenW-CRM, and MenY-CRM DS and for the primary containers. They evaluated if the DSs manufacturing processes would contribute to (b) (4); whether the process conditions ((b) (4)) can lead to (b) (4); if the processes include operations that lead to (b) (4) (the MenACWY Lyo DSs manufacturing processes do); and if the potential impurities introduced by raw materials, process inputs, and single-use components would not be cleared by the process. GSK concludes that for MenACWY Lyo DS and for the DP the risk for the presence of (b) (4) is negligible and that they have not found any source of (b) (4).
- (b) (4) Risk Assessment MenB Liquid (MH): Please see section 3.2.P.5.5 Characterization of Impurities (page 223 of this memo).
- Documents approved under MENVEO supplements:
  - (b) (4)
- Documents approved under BEXSERO supplements:
  - (b) (4)
- Documents GSK submitted in STN 125819/0.13 (dated 8 July 2024) in response to our information request dated 25 June 2024: I reviewed the following documents as part of my review of Amendment 13:

- (b) (4) [REDACTED]
- Documents GSK submitted in Amendment STN 125819/0.37, (dated 4 November 2024) in response to our information request dated 28 October 2024):
  - (b) (4) [REDACTED]

**v. Comparability Protocols**

GSK provided the following documentation:

- **DS and DSI (submitted under MENVEO):**

**Reviewer comment (MB):** All the protocols I present below were approved under MENVEO. For details on the protocols and their review I refer the reader to the review memoranda for the specific supplements in which these protocols were approved, listed in the table below. Master comparability protocol VA-0000552345, for qualification of (b) (4) for the Identity test, is reviewed under 3.2.S.5 Reference Standards or Materials of this memorandum.

(b) (4)

(b) (4)

- **MenACWY Lyo DP:**

- (b) (4)

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



For the batch to be used as PC it must satisfy the following criteria:

- Conform with specifications approved at the time of testing.
- Be representative of the approved manufacturing process.
- Any deviation that occurred during manufacturing should be closed and should be considered not to have impacted product quality.

In cases of a supply impact that limits available batches, GSK may select batches that do not meet the above criteria. In such cases they will submit the qualification as a CBE-30.

The PC is considered qualified if:

- (b) (4)

**Reviewer comment (MB):** This protocol was reviewed in the context of MenACWY Liquid under STN 125300/896 (approved 20 May 2024).

- Sucrose Content:

(b) (4)

**Reviewer comment (MB):** *I consider that the system suitability, analytical session validity and the qualification criteria described in this CP is adequate for qualification of new PCs.*

- (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

- **MenABCWY RV**

- Pyrogenicity:

(b) (4)

[REDACTED]

For a BEXSERO batch to qualify as a reference standard for the assay it must satisfy the following criteria:

- (b) (4)

[REDACTED]

(b) (4)



**Reviewer comment (MH):** All the protocols I present below were approved under BEXSERO. For details on the protocols and their review I refer the reader to the review memoranda for the specific supplements in which these protocols were approved.

**Table 37. Submitted comparability protocols approved under BEXSERO.**

(b) (4)

In **STN 125819/0.71** (07 February 2025) GSK clarified that all changes made using the comparability protocols listed in this section will be submitted under the Annual Report except for VA-0000166988 which will report under CBE-30. GSK will submit updated CPs reflecting these reporting categories in their first Annual Report.

#### **Other eCTD Modules**

##### **Module 1**

#### **A. Environmental Assessment or Claim of Categorical Exclusion**

A claim of categorical exclusion has been submitted under **21 CFR 25.31(c)**. FDA concludes that this product occurs naturally in the environment, and approval of this BLA supplement does not significantly alter the concentration or distribution of the

substance, its metabolites, or degradation products in the environment, and no extraordinary circumstances exist. The categorical exclusion claim is accepted.

## **B. Reference Product Designation Request**

The applicant filed a claim of exclusivity on 15 February 2024, claiming there are no licensed biological products that are structurally related to PENMENVY for which they or one of their affiliates, licensors, predecessors in interest, or related entities is the current or previous license holder. GSK has two other licensed meningococcal vaccine products. They believe that PENMENVY is not structurally related to MENVEO or BEXSERO because PENMENVY has additional antigens relative to each; MENVEO lacks the MenB antigens, and BEXSERO lacks the MenA-, MenC-, MenW-, and MenY-CRM conjugates. For these reasons, the applicant believes that PENMENVY will have a difference in potency than either MENVEO or BEXSERO.

GSK also described Wyeth's MenB vaccine Trumenba, Pfizer Ireland's MenABCWY vaccine Penbraya, and Sanofi Pasteur's MenACWY vaccine Menactra. PENMENVY differs from these vaccines as follows:

- Trumenba: PENMENVY has additional MenB antigens (NadA, NHBP, fHBP, and purified outer membrane vesicles with PorA as the immunodominant antigen) as well as the oligosaccharide conjugates.
- Penbraya: PENMENVY has additional MenB antigens, as described in the bullet above. The MenA, MenC, MenW, and MenY polysaccharides are also conjugated to CRM197, whereas in Penmenvy they are conjugated to tetanus toxoid. The two vaccines also use different conjugation chemistries.
- Menactra: PENMENVY has MenB antigens, which Menactra lacks as it is a MenACWY vaccine. Additionally, the four polysaccharide antigens are conjugated to diphtheria toxoid in Menactra, whereas PENMENVY uses CRM197.

Upon finalization of this memo, the Reference Product Exclusivity Board had not yet met to discuss. If approved, the product will be designated as a reference product and the associated exclusivity periods will be based on the first date of approval.

## **C. Labeling Review**

### **Full Prescribing Information (PI):**

Prescribing information in the package insert (PI) contains information about the dosage, form, and strength of PENMENVY, a description of its contents, a summary of the clinical pharmacology supporting its indication and instructions for storage and handling. In brief, the PI indicates that PENMENVY is a suspension for injection as a single 0.5 mL dose after reconstitution. MenACWY Lyo comprises oligosaccharides from serogroups A, C, W, and Y, each individually conjugated to CRM197, which are (b) (4), filled into a glass vial, and lyophilized. The MenB component comprises three recombinant proteins, as well as outer membrane vesicles (OMV) from serogroup B, as a liquid formulation within a prefilled syringe (PFS).

PENMENVY is supplied with the two components (MenACWY Lyo vial and MenB Liquid PFS) co-packaged in a carton of 10 doses without needles. The contents of the PFS are used to reconstitute MenACWY Lyo, and then the reconstituted vaccine is drawn back into the PFS for administration. PENMENVY must be used immediately.

Vaccination with PENMENVY induces an immunological response that includes production of antibodies to the MenA, MenC, MenW, and MenY polysaccharides as well as to the MenB proteins (both recombinant and those present in the OMV). These antibodies have bactericidal activity and leads to complement-mediated, antibody-dependent killing of the *N. meningitidis* serogroups covered by PENMENVY.

#### **Carton and Container Label:**

The carton and container labels reflect the information provided in Section 3.2.P.1 *Description and Composition of the Drug Product* and are acceptable.

### **Modules 4 and 5**

Analytical Procedures and Validation of Analytical Procedures for Assessment of Clinical and Animal Study Endpoints (**Reviewed by KM**)

#### **Module 4**

To demonstrate immunogenicity of PENMENVY, GSK conducted pre-clinical studies in mice and rabbits, with total IgG antibody and functional antibody titers (i.e., bactericidal activity) measured. For a comprehensive review of pre-clinical data, see Section 5.1 *Nonclinical Assessment of Potential Effectiveness* in the CBER Integrated Review memo.

#### **Module 5**

GSK utilized several different serological assays to evaluate clinical endpoints during Phase 2 and Phase 3 development of PENMENVY, including human complement serum bactericidal assays (hSBAs), ELISAs, (b) (4) assay. In Phase 2, the applicant employed an ELISA to calculate (b) (4) a high-throughput hSBA (HT-hSBA) to determine (b) (4) tilt hSBA was also used in Phase 2 study V102\_02. Prior to initiation of Phase 3 testing, the (b) (4)

While secondary endpoints in the Phase 3 pivotal study V72\_72 included immunogenicity assessments as measured via the tilt (b) (4), GSK employed a third serological assay, the endogenous complement hSBA (enc-hSBA), to analyze vaccine effectiveness (i.e., breadth of coverage) as a primary

(b) (4)

. The utility of the enc-hSBA in measuring vaccine effectiveness was first tested in Phase 2 clinical study V102\_16 and its corresponding extension study V102\_16E1; groups of participants administered BEXSERO alone served as a comparator. Immunogenicity comparisons between PENMENVY and BEXSERO were also examined in the V1026\_16 studies using the HT-hSBA, in addition to the Phase 2 study V102\_15 and its extension study V102\_15E1; the enc-hSBA was not used in the latter studies. The development, qualification and/or validation, and stability of the ECL assay, the tilt (b) (4) hSBAs, and the enc-hSBA are described in detail below as pertains to their use in evaluation of serological data from Phase 3 studies V72\_72 and MenABCWY-019. For a description on the development of the HT-hSBA as it pertains to assessment of supportive Phase 2 data, see the CMC memo to sBLA 125546/1058.

*Serological Assay Development*

enc-hSBA

(b) (4)

