

**CBER DMPQ CMC/Facility BLA Review Memorandum**

**BLA STN 125770**

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

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1. **BLA#:** STN 125770

2. **APPLICANT:** Pfizer Ireland Pharmaceuticals, US License Number 2060

3. **PRODUCT NAME/PRODUCT TYPE**

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

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

a. **Pharmacological category**

Vaccine

b. **Dosage form**

Suspension for injection

c. **Strength/Potency**

0.5 mL

d. **Route of administration**

Intramuscular

e. **Indication(s)**

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

5. **MAJOR MILESTONES**

Received: October 21, 2022

First Committee Meeting: November 11, 2022

Filing Meeting: December 5, 2022

Filing Action: December 20, 2022

PDUFA ADD: October 20, 2023

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

Reviewer/Affiliation	Section/Subject Matter
Jared Greenleaf, CSO, OCBQ/DMPQ/MRB1	3.2.S Drug substance (b) (4) 3.2.P Drug Product • MenACWY-TT 3.2.A.1 Facilities and Equipment: • (b) (4)

Reviewer/Affiliation	Section/Subject Matter
	<ul style="list-style-type: none"> <li>• (b) (4)</li> </ul> 3.2.R Regional Information <ul style="list-style-type: none"> <li>• (b) (4)</li> </ul>
Kathleen Jones, Lead CSO, OCBQ/DMPQ/MRB1	3.2.S Drug Substance (b) (4) 3.2.R Regional Information <ul style="list-style-type: none"> <li>• Comparability protocol for (b) (4)</li> </ul>
Miriam Ngundi, CSO, OCBQ/DMPQ/MRB1	3.2.P Drug Product <ul style="list-style-type: none"> <li>• MnB Bivalent (b) (4)</li> </ul> 3.2.A.1 Facilities and Equipment <ul style="list-style-type: none"> <li>• (b) (4)</li> </ul>
Nicole Li, Lead CSO, OCBQ/DMPQ	3.2.P Drug Product <ul style="list-style-type: none"> <li>• MenABCWY</li> </ul> 3.2.A.1 Facilities and Equipment (b) (4) 3.2.R Regional Information <ul style="list-style-type: none"> <li>• 21 CFR Part 4 Description</li> </ul>

**7. SUBMISSION(S) REVIEWED**

Date Received	Submission	Comments/ Status
October 21, 2022	STN 125770/0	Original Submission
January 13, 2023	Amendment STN 125770/0.3 (Response to December 16, 2022 information request (IR))	CMC comments pertaining to (b) (4) (b) (4) DS; updates to 3.2.S.2.2 and 3.2.S.2.5, and 3.2.R (SOPs)
March 17, 2023	Amendment STN 125770/0.10 (Response to March 3, 2023 IR)	Additional facility information needed

Date Received	Submission	Comments/ Status
May 5, 2023	STN 125770/0.15 (Response to April 24, 2023 IR)	MnB (b) (4) PPQ microbial acceptance criteria; MnB (b) (4) shipping validation; MnB (b) (4) stability updates / reviewed
July 28, 2023	STN 125770/0.26	MnB DP hold time validation, media fills, container reject rates, buffer microbial acceptance criterion

## 8. REVIEWER SUMMARY AND RECOMMENDATION

### I. EXECUTIVE SUMMARY

Pfizer submitted Biologics License Application (BLA) 125770/0 to support licensure of PENBRAYA, intended to prevent invasive disease caused by *Neisseria meningitidis* groups A, B, C, W, and Y in individuals 10 through 25 years of age. DMPQ reviewed and evaluated the (b) (4) the (b) (4) and drug products (DP) manufacturing process and facilities proposed for use to manufacture PENBRAYA. Coverage of information in this review memo includes data to validate and support the consistency of the manufacturing process and product quality; facility information which includes utilities, cross-contamination prevention measures, and maintenance of controlled environments; and equipment for use in manufacturing including qualification, cleaning and sterilization, and types of equipment used (i.e., dedicated or shared, multi-use or single-use).

The MenABCWY vaccine is composed of two DP components; MenACWY-TT and MnB Bivalent (b) (4) (previously licensed as Trumenba; STN 125549/0). MenACWY-TT is provided as a sterile lyophilized power for injection supplied in a 2 mL glass vial. MnB is provided as a sterile liquid suspension pre-filled into 1 mL syringes. The MenABCWY DP is generated by reconstituting the MenACWY-TT DP with the MnB DP in a single use prefilled syringe using a vial adapter and the entire extractable content is withdrawn to enable a dose of 0.5 mL for intramuscular administration. A 0.5 mL dose of MenABCWY vaccine delivers MnB (b) (4) subfamily A and B proteins at 60 µg /subfamily and MenAAH-TT, MenCAH-TT, MenW-TT, and MenY-TT at 5 µg/serogroup. The MenABCWY DP is single use and contains no preservatives.

The MenACWY-TT DP component is a sterile lyophilized powder for injection composed of the purified polysaccharides of *Neisseria meningitidis* serogroups A, C, W-135, and Y, each conjugated to tetanus toxoid (TT) (b) (4) (b) (4) respectively. The (b) (4) MenACWY-TT DP component is filled at a concentration of (b) (4) serogroup into vials for reconstitution with MnB to deliver 5 µg (b) (4) of each serogroup per dose (0.5 mL).

The MnB Bivalent (b) (4) DP component is a sterile liquid suspension composed of (b) (4) subfamily A and B proteins formulated at 120 µg/mL/subfamily. MnB was designed to reconstitute the lyophilized MenACWT-TT DP component through a vial adapter to obtain the final MenABCWY vaccine.

The lyophilized meningococcal groups A, C, W, and Y polysaccharide tetanus toxoid (TT) conjugate component (lyophilized MenACWY-TT component) are manufactured at (b) (4)

and (b) (4)  
(b) (4) and formulated, filled, and lyophilized at (b) (4)  
(b) (4)

The meningococcal serogroup B factor H binding protein component (MenB component, also referred to as MnB Bivalent (b) (4) or (b) (4) MnB (b) (4)-MnB)) is manufactured at (b) (4) and filled at (b) (4)

The lyophilized MenACWY component and the MenB component are labeled and packaged with the vial adapter to form the final kitted product, Meningococcal Groups A, B, C, W and Y Vaccine (PENBRAYA), at (b) (4)

(b) (4)

DMPQ waived inspections of the following facilities:

(b) (4)

The basis for the waiver justification is documented in a separate Inspection Waiver Memorandum which was uploaded to CBER Connect dossier for the subject BLA.

Based on the information submitted to BLA 125770/0 along with the associated DMPQ purview amendments and in conjunction with the inspectional compliance history evaluations, the production process, facilities, equipment, and controls appear acceptable for the licensure of PENBRAYA, and approval is recommended.

**J. RECOMMENDATION**

**K. APPROVAL**

Based on the information provided in the original application and amendments, DMPQ recommends the approval of Meningococcal Groups A, B, C, W and Y Vaccine with inspectional recommendations.

The lyophilized meningococcal groups A, C, W, and Y polysaccharide tetanus toxoid (TT) conjugate component (lyophilized MenACWY-TT component) will be manufactured at (b) (4)

(b) (4) and formulated, filled, and lyophilized at (b) (4)

The meningococcal serogroup B factor H binding protein component (MenB component, also referred to as MnB Bivalent (b) (4) or (b) (4) MnB (b) (4) MnB)) will be manufactured at (b) (4) (b) (4) and filled at (b) (4)

The lyophilized MenACWY component and the MenB component will be labeled and packaged with the vial adapter to form the final kitted product, Meningococcal Groups A, B, C, W and Y Vaccine (PENBRAYA), at (b) (4) (b) (4)

The approval includes the following comparability protocols that are under DMPQ's purview:

- Lifetime extension for (b) (4) (b) (4)
- Lifetime extension for (b) (4)
- Lifetime extensions for (b) (4) (b) (4)
- (b) (4)
- (b) (4)

The proposal to report the data from the comparability protocols in Annual Report appears acceptable; however, the final determination on the reporting category is the responsibility of the Office of Vaccines Research and Review (OVRP).

CBER understands the following inspectional recommendations may or may not be taken (based on risk and available resources) and is not requesting documentation to be submitted as evidence of completion. The inspectional recommendations are as follows:

(b) (4)

:

1. During execution of (b) (4) studies at (b) (4) several deviations were encountered. The applicant submitted a comparability protocol that details plan to provide (b) (4) data when available. Please review (b) (4) cleaning, sanitization, and storage procedures to ensure that (b) (4) remains in a state of control.
2. To verify the (b) (4) remain in a qualified state that is reflective of the sterilization process (b) (4) (b) (4) used to manufacture the MnB (b) (4) subfamily A and B (b) (4) and that the sterilization processes are periodically reviewed to ensure the processes remain validated

(b) (4)

3. To verify the (b) (4) remains in a qualified state that is reflective of the sterilization process of non-critical product contact parts used to manufacture (b) (4)
4. The (b) (4) acceptance criterion for in-process samples, performed during the (b) (4) processes, are significantly higher than the reported test results. Please verify that as part of current good manufacturing practices, the in-process limits are being evaluated and tightened to reflect process capability.
5. As (b) (4) is taken post (b) (4) for multiple manufacturing steps of the conjugated polysaccharide (b) (4) please verify that any product impact assessment due to an environmental excursion is appropriately conducted as the firm cannot rely on the (b) (4) results as a surrogate to product impact.

(b) (4)

6. The specification for (b) (4) in-process testing performed during (b) (4) (b) (4) process validation at (b) (4) was increased from (b) (4) (b) (4). Please review the relevant in-process test results and determine if the applicant can tighten the (b) (4) in-process specification with consideration of process capabilities.

## II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Jared Greenleaf, CSO, OCBQ/DMPQ/MRB1	Concur	
Kathleen Jones, Lead CSO, OCBQ/DMPQ/MRB1	Concur	
Miriam Ngundi, CSO, OCBQ/DMPQ/MRB1	Concur	
Nicole Li, Lead CSO, OCBQ/DMPQ	Concur	
Lori Peters, Branch Chief, OCBQ/DMPQ/MRB1	Concur	
For Carolyn Renshaw, Director, OCBQ/DMPQ	Concur	



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**Module 3**

**3.2.S DRUG SUBSTANCE (b) (4)**

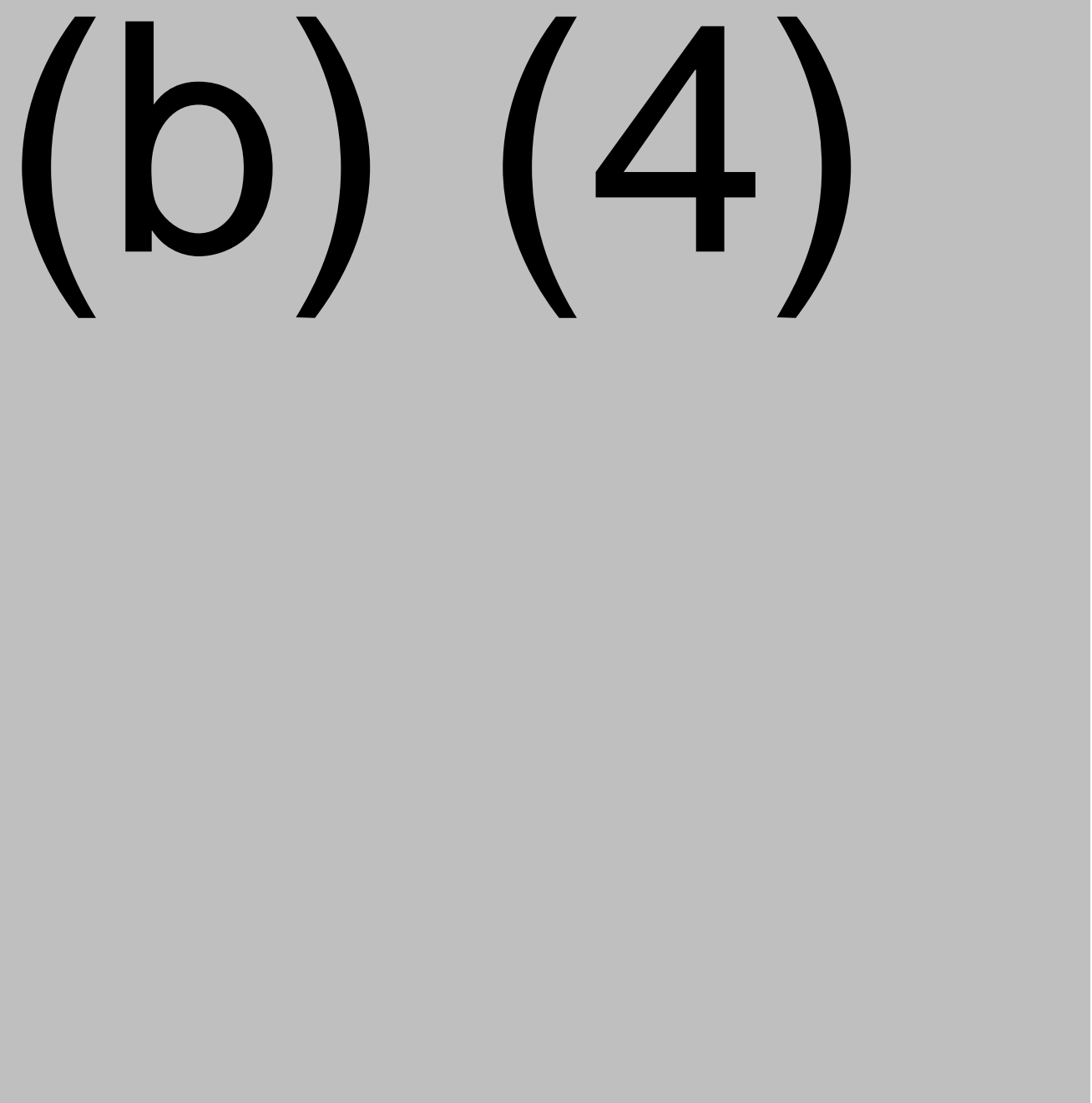
(b) (4)

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**3.2.S.2 Manufacture**

**3.2.S.2.1 Manufacturer(s)**

(b) (4)

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(b) (4)

**3.2.S.2.2 Description of Manufacturing Process**

(b) (4)

15 pages were determined to be not releasable: (b)(4)

### 3.2.P DRUG PRODUCT (MnB Bivalent (b) (4))

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

The MnB bivalent (b) (4) drug product (DP) component is a sterile liquid suspension of (b) (4) subfamily A and B proteins. The MnB bivalent (b) (4) DP is also called (b) (4) -MnB). (b) (4) -MnB is filled into a 1 mL syringe, with a target volume of (b) (4) for the extractable volume of (b) (4). (b) (4) -MnB is used to reconstitute the lyophilized MenACWY-TT DP component using a co-packaged vial adapter to form the final MenABCWY vaccine. In Table 3.2.P.1-1, Pfizer provided the composition of the MnB bivalent (b) (4) component and the function of each ingredient.

#### 3.2.P.2.5 Microbiological Attributes

Manufacture of (b) (4) -MnB includes sterile filtration and aseptic processing. Release specifications include sterility testing (per (b) (4)) endotoxin testing (per (b) (4)) and CCIT (b) (4)).

*Container Closure Integrity Test (CCIT):* (b) (4)

(b) (4)

**Reviewer's comment:** The information provided appears acceptable. Microbial test methods are (b) (4) or qualified (CCIT). The results for the qualification of the container closure system met all acceptance criteria. (b) (4) syringe/plunger stopper combinations were used for the PPQ lots to support the BLA. The (b) (4) syringe with (b) (4) plunger stopper combination was not used. The PPQ study also used the (b) (4) syringe with (b) (4) (b) (4) plunger stopper combination. The (b) (4) and (b) (4) plunger stoppers are identical i.e., (b) (4) (b) (4) latex-free gray chlorobutyl rubber (elastomer) (b) (4) (b) (4) and latex-free formulated and (b) (4) (b) (4). There is no difference in dimensions between the stoppers supplied by (b) (4) and (b) (4).



**3.2.P.3 Manufacture**

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

Location	Responsibility
(b)	(4)

**3.2.P.3.3 Description of Manufacturing Process, and 3.2.P.3.4 Controls of Critical Steps and Intermediates**

(b)	(4)
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2 pages have been determined to be not releasable: (b)(4)

(b) (4)

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

(b) (4)

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

(b) (4)

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

(b) (4)

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

(b) (4)

(b) (4)

#### **3.2.P.5.4 Batch Analyses**

Pfizer provided the batch analyses for (b) (4)-MnB DP component lots (engineering, stability, Phase 2b/3 clinical/stability), and process validation/primary stability). Additionally, the sponsor provided the batch analyses for (b) (4) Trumenba DP lots. The results for all the lots met the acceptance criteria for endotoxin (b) (4) and sterility (no growth observed).

**Reviewer's comment:** The information provided appears acceptable. All bacterial endotoxin and sterility results met the release acceptance criteria for all lots. The data appear to indicate that a sterile (b) (4)-MnB DP component can be consistently manufactured at (b) (4). Review of the other test results is deferred to OVR.

### 3.2.P.7 Container Closure System

The primary container closure system (CSS) for the (b) (4) MnB pre-filled syringe consists of the components:

- Syringe (product contact): 1 mL Type (b) (4) borosilicate glass with barrel (b) (4). The syringes are supplied by (b) (4). The (b) (4) syringe is pre-assembled with a Plastic Rigid Tip Cap (PRTC), and the (b) (4) syringe is pre-assembled with a (b) (4) Rigid Cap. Both tip cap assemblies include a non-product contact polycarbonate Luer lock adapter, a non-product contact polypropylene rigid cap, and a product contact elastomeric tip cap. The tip cap elastomer is (b) (4) latex-free, gray synthetic isoprene/bromobutyl blend rubber and is manufactured by (b) (4).
- Plunger stopper (product contact): 1 – 3 mL stopper made of (b) (4) latex-free gray chlorobutyl rubber elastomer (b) (4). The plunger stoppers are formulated and (b) (4) packaged, and supplied by (b) (4). For the plunger stoppers supplied by (b) (4), is performed at (b) (4) respectively.
- Plunger rod (non-product contact): Polypropylene plunger rod.
- Finger grip (non-product contact): Polypropylene finger grip (backstop).

Pfizer stated that the single-use syringes meet (b) (4) requirements for Type (b) (4) borosilicate glass containers, as well as (b) (4) requirements for glass barrels for injectables and sterilized sub-assembled syringes ready for filling. The tip cap elastomer meets the requirements of (b) (4). (b) (4) Pfizer provided the dimensions all components of the syringe assembly (glass barrel, tip cap, and luer-lock adaptor) as well as representative drawings for syringe barrel, and tip cap.

Pfizer stated that the (b) (4) of the syringes by (b) (4) is performed at the supplier according to (b) (4) with a (b) (4). The syringes are received at the DP manufacturing site (b) (4) in ready-to-use tubs. In Tables 3.2.P.7-2 and 3.2.P.7-3, Pfizer provided the syringe manufacturing and (b) (4) sites.

The following tests are performed on the syringe barrels at the DP component manufacturing site (in-house testing). Alternatively, the supplier's certificate may be accepted for one or more tests.

- Visual inspection of the syringe package: Performed per lot
- Visual inspection of the barrel: Performed per lot
- Physical inspection of the barrel: Performed per lot
- Functionality testing of syringe: Performed per lot
- (b) (4) test: Performed per lot
- (b) (4) Type (b) (4) glass tests: Manufacturer's certification is accepted per lot. (b) (4) verification is performed on (b) (4) to ensure testing requirements are met.
- (b) (4) Manufacturer's certification is accepted per lot. (b) (4) verification is performed on (b) (4) to ensure testing requirements are met.
- Sterility: Manufacturer's certification is accepted per lot. (b) (4) verification is performed on (b) (4) to ensure testing requirements are met.
- Endotoxin: Manufacturer's certification is accepted per lot. (b) (4) verification is performed on one lot per year to ensure testing requirements are met.

The plunger stoppers are formulated (b) (4) by the manufacture and (b) (4) (b) (4) to meet (b) (4) Pfizer provided the dimensions and the representative drawing of the plunger stopper. In Table 3.2.P.7-8, Pfizer provided the plunger stoppers manufacturing, processing, and sterilization sites. The following tests are performed on the plunger stoppers. Alternatively, the supplier's certificate may be used for one or more tests.

- Identification of (b) (4) Performed per lot.
- Visual inspection of package (bags) and stoppers: Performed per lot.
- Sterility: Manufacturer's certification is accepted per lot.

**Reviewer's comment:** *The information provided on the primary container closure system for the (b) (4)-MnB DP component appears acceptable.*

### 3.2.P.8 Stability

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

The proposed shelf life of the (b) (4)-MnB DP component is 24 months when stored at the recommended temperature of 2 – 8 °C in (b) (4) or (b) (4). The shelf-life claim is based on 24 months of real time stability data from (b) (4) primary stability lots of (b) (4) MnB stored at the long-term condition of 5 ± 3 °C in the tip-up orientation

Pfizer provided the primary stability information for the (b) (4) (b) (4)-MnB DP component process validation lots (b) (4) when stored under the following conditions:

- Long term: 5 ± 3 °C
- Accelerated: (b) (4)
- (b) (4)



(b) (4)

(b) (4) lots were filled in the (b) (4) syringe type while (b) (4) (b) (4) was filled in (b) (4) syringe. All four (b) (4) MnB DP component lots were assessed at long term, accelerated and (b) (4) was assessed on lot (b) (4) only.

Pfizer also provided supportive stability studies based on long term and accelerated studies of (b) (4)-MnB DP component lots (b) (4) and (b) (4) (Phase 2b/3 and stability, (b) (4) ) as well as long term studies of (b) (4) Trumenba DP lots (b) (4) used for MnB (b) (4) comparability and stability studies.

During the stability studies the test for CCI, endotoxin and sterility are performed at the listed intervals, and the results for available data (\*) met the indicated acceptance criteria for lots:

(b) (4)

**Reviewer's comment:** All results for the tested DP met the acceptance criteria for CCIT, endotoxin, and sterility, and the information appears acceptable. The long-term stability data limited to CCIT, endotoxin, and sterility from the process validation lots appear supportive of the 24 months shelf life; however, final determination on the overall stability of (b) (4) MenB is the responsibility of OVR. Pfizer's post-approval stability protocol indicated that CCIT will be tested at 0, 12, 24, (b) (4) and (b) (4) timepoints while sterility and endotoxin will be tested at 0

*and end of shelf life. DMPQ defers the review of all other stability testing to OVR.*

**3.2.S DRUG SUBSTANCE (b) (4)**

**(b) (4)**

**3.2.S.2 Manufacture**

**3.2.S.2.1 Manufacturer(s)**

**(b) (4)**

65 pages have been determined to be not releasable: (b)(4)

(b) (4)

### 3.2.P DRUG PRODUCT (MenACWY-TT) (Lyophilized)

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

The MenACWY-TT DP component is a sterile lyophilized powder for injection composed of the purified polysaccharides of *Neisseria meningitidis* serogroups A, C, W, and Y, conjugated to tetanus toxoid. The drug product component is formulated in (b) (4) trometamol buffer containing (b) (4) sucrose, at pH (b) (4). Each lyophilized DP component vial of MenACWY-TT is designed to deliver 5 µg of each conjugate serogroup in the reconstituted 0.5 mL dose.

Each DP vial is filled with 0.5 mL of (b) (4) DP prior to lyophilization. To account for the (b) (4) there is a (b) (4) manufacturing (b) (4) of the serogroups (i.e., (b) (4) to ensure 5 µg of each serogroup is delivered to the patient. The bulk DP component is filled at a concentration of (b) (4) into vials for reconstitution with (b) (4)-MnB to ensure a final dose concentration of (b) (4) (b) (4).

#### 3.2.P.2 Pharmaceutical Development

##### 3.2.P.2.4 Container Closure System

The MenACWY-TT DP is filled into 2 mL Type (b) (4) clear borosilicate glass vials that are manufactured by (b) (4) or Medica (b) (4) (b) (4). The vial is closed with a 13 mm siliconized bromobutyl-rubber lyophilization stopper and an aluminum seal with a tamper-evident polypropylene flip-off cap. The stopper is manufactured by (b) (4) and the crimp seal is manufactured by (b) (4).

Pfizer assessed the comparability of the (b) (4) vials in terms of dimensional comparability, material of construction, safety (biological activity and biocompatibility), product stability, and product performance requirements. Pfizer states that vials from both suppliers were used to manufacture clinical material.

The glass vials meet the (b) (4) requirements for chemical testing for Type (b) (4) glass containers. The stoppers meet (b) (4) (b) (4) requirements for function tests of (b) (4) capacity.

Reference Section 3.2.P.7 Container Closure System for descriptions of container closure and stopper quality control testing.

**Reviewer's comment:** *These vials are used interchangeably for another FDA product (STN (b) (4)). The evaluation of suitability, biological activity, chemical resistance, extractables, leachables, and photostability is deferred to OVR.*

### 3.2.P.2.5 Microbiological Attributes

The manufacturing process utilizes pre-sterilized raw materials and supplies, HEPA-filtered, classified production areas, and personnel gowning controls.

Final product sterility testing is performed according to (b) (4) A (b) (4) examination of the drug product formulation determined that it is non-inhibitory. Bacterial endotoxin release testing is performed according to (b) (4)

Qualification of the container closure system was performed via (b) (4) CCIT method. Method qualification consisted of (b) (4) runs, with (b) (4) positive controls and (b) (4) negative controls. The acceptance criteria were observed (b) (4) positive control vials and (b) (4) negative control vials. All acceptance criteria were met.

(b) (4) testing of product vials consisted of (b) (4) runs: (b) (4) minimum (b) (4) run (b) (4) and (b) (4) maximum (b) (4) run (b) (4). Each run was performed with (b) (4), (b) (4) positive controls, and (b) (4) negative controls. All acceptance criteria were met.

### 3.2.P.3 Manufacture

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

Location	Responsibility
(b) (4)	(b) (4)

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

(b) (4)

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

#### 3.2.P.5.1 Specification(s), 3.2.P.5.2 Analytical Procedure(s), and 3.2.P.5.3 Validation of Analytical Procedure(s)

The sterility analytical procedure used for release is performed per (b) (4) (b) (4). The endotoxin analytical procedure is performed per (b) (4) (b) (4) using the (b) (4) method. The endotoxin release specification is (b) (4). CCIT is performed (b) (4) on stability in lieu of sterility, using the (b) (4) test method.

**Reviewer's comment:** CCIT is performed via the (b) (4) method. Method development and review of the initial CCIT qualification is provided in Section 3.2.P.2.5 Microbiological Attributes. Excluding CCIT, review of method validation is deferred to the DBSQC reviewer.

#### 3.2.P.5.4 Batch Analyses

The applicant provided batch release data from (b) (4) lots, including sublots, of MenACWY-TT DP manufactured at (b) (4) from (b) (4) (b) (4). The lots were used for clinical (phase 2b/3), confirmatory, process validation, and primary stability purposes. The confirmatory parent lot and (b) (4) process validation parent lots were split into sublots to cover the (b) (4) lyophilizers (b) (4). The following sublots were placed on stability for monitoring:

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

**Reviewer's comment:** All sterility and bacterial endotoxin results met the release acceptance criteria for all lots. The information provided appears acceptable. Review of the other test results is deferred to OVR.

### 3.2.P.7 Container Closure System

The MenACWY-TT DP is filled into 2 mL Type (b) (4) clear borosilicate glass vials that are manufactured by (b) (4). The vial is closed with a 13 mm siliconized (b) (4) elastomer (bromobutyl-rubber) lyophilization stopper and an aluminum seal with a tamper-evident polypropylene flip-off cap. The lyophilization stopper meets the (b) (4) requirements. The stopper is manufactured by (b) (4) and the crimp seal is manufactured by (b) (4).

The applicant provided dimensional limits and representative drawings of the (b) (4) vials, the (b) (4) stopper, and the (b) (4) crimp seal. Upon receipt, each lot of glass vials and stoppers are visually inspected. Verification of critical dimensions is performed on a minimum of (b) (4). The supplier's certificate is accepted for compendial compliance. Each lot of crimp seals are visually and physically inspected.

**Reviewer's comment:** Based on the drawings, the critical dimensions (b) (4) are identical. The CCIT method (b) (4) validation is found in Section 3.2.P.2.5 Microbial Attributes above. The information provided appears acceptable.

### 3.2.P.8 Stability

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

The proposed shelf life for MenACWY-TT DP component is 18 months when stored at the recommended temperature of 2 – 8°C.

The primary stability studies consisted of long-term, accelerated, (b) (4) and (b) (4) studies. All primary stability studies have been completed except for the long-term studies. At least 18 months of data were provided for the long-term studies. All stability samples were stored in the (b) (4) position. The studies used the following conditions:

- Long-term: 5 ± 3 °C for (b) (4)
- Accelerated: (b) (4)
- (b) (4)
- (b) (4)

The supportive stability studies consisted of long-term, accelerated, and (b) (4) studies. The long-term and accelerated studies include the same storage conditions as the primary stability studies. Confirmatory batch (b) (4) and process validation batches (b) (4) were used for the supportive stability studies. The accelerated studies have been completed. The long-term and (b) (4) studies



are ongoing. Confirmatory sublots (b) (4) were enrolled in long-term and accelerated studies; 3 months of data were provided. The supportive stability lots covered lyophilizers (b) (4) and included (b) (4). The following conditions were used for the (b) (4) studies:

(b) (4)

**Reviewer's comment:** All acceptance criteria were met. The 12-month CCIT result for lot (b) (4) was listed as not reportable because the result was not reviewed on time; however, a passing result was reported at the (b) (4) month time point. Based on the primary stability results limited to sterility, CCIT, and endotoxin, the 18-month proposed shelf life appears acceptable; however, final determination of the proposed shelf-life is the responsibility of OVR. Review of stability data not within DMPQ purview is deferred to OVR.

### 3.2.P DRUG PRODUCT (MenABCWY)

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

The MenABCWY vaccine DP is a co-packaged kit that is composed of the following:

- A 13 mm sterile polycarbonate Luer lock vial adapter (siliconized, (b) (4) by (b) (4) individually packaged) purchased from (b) (4) (b) (4)
- MenACWY-TT DP component: a sterile lyophilized powder for injection supplied in a 2 mL glass vial
- MnB Bivalent (b) (4) -MnB) DP component: a sterile liquid suspension pre-filled into 1 mL syringes

Prior to use, the MenABCWY DP is generated by reconstituting the MenACWY TT DP component with the (b) (4)-MnB DP component in a single-use PFS using a vial adapter, and the entire extractable content is withdrawn to enable a dose of 0.5 mL for intramuscular administration. A 0.5 mL dose of the MenABCWY vaccine delivers (b) (4) subfamily A and B proteins at 60 µg /subfamily and MenA<sub>AH</sub>-TT, MenC<sub>AH</sub>-TT, MenW-TT, and MenY-TT at 5 µg/serogroup at pH 6.0 and uses the same 1 mL syringe that contained the (b) (4)-MnB. The MenABCWY DP contains no preservatives and is for single use only.

To account for the overall (b) (4) - (b) (4) volume of the vial and dose preparation components, there is a (b) (4) manufacturing (b) (4) of the concentration of the MenA<sub>AH</sub>-TT, MenC<sub>AH</sub>-TT, MenW-TT, and MenY-TT serogroups in the MenACWY-TT DP component vial.

### 3.2.P.3 Manufacture

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

Location	Responsibility
(b) (4)	(4)

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

(b) (4)	(4)
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3 pages have been determined to be not releasable: (b)(4)

(b) (4)

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

**Reviewer's comment:** The MenABCWY vaccine specifications are product specific and deferred to OVR.

### 3.2.P.7 Container Closure System

**Reviewer's comment:** The MenABCWY vaccine consists of the MenACWY-TT and (b) (4) MnB DP components and their container closure systems were reviewed in their respective DP component sections.

### 3.2.P.8 Stability

**Reviewer's comment:** No formal stability studies have been conducted on MenABCWY vaccine to date. However, post-approval, at least (b) (4) MenABCWY

*vaccine lot will be enrolled in the stability program at long-term condition of (b) (4) each year the product is manufactured. Immediate product specific testing will be performed on the reconstituted MenACWY-TT with (b) (4)-MnB. The MenABCWY vaccine stability program is deferred to OVR.*

### 3.2.A APPENDICES

The following table includes a full listing of all facilities associated with the BLA submission.

(b) (4)

2 pages have been determined to be not releasable: (b)(4)

(b) (4)

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

(b) (4)

9 pages have been determined to be not releasable: (b)(4)



(b) (4)

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

The meningococcal-tetanus toxoid conjugate (b) (4) and the MnB bivalent (b) (4) DP component are manufactured at the (b) (4) located at the (b) (4) (b) (4). Additionally, the facility is used for the (b) (4), and DP testing and storage. The site is a multi-product facility that manufactures and tests commercial and clinical vaccine products.

(b) (4)

3 pages have been determined to be not releasable: (b)(4)

*The disinfectants used in the facility appear acceptable as the (b) (4) building is multiproduct and is used to manufacture Trumenba, which has the same formulation as MnB bivalent (b) (4) DP. Additionally, the media fill information appears to support the aseptic operations to provide sterile products. Furthermore, the media fills conducted since 2019 were reviewed during the January 2023 surveillance inspection, including the (b) (4) media fills that were ongoing during the surveillance inspection.*

#### Computer systems

The main systems used to manufacture the meningococcal – tetanus toxoid conjugates for serogroup A, C, W, and Y (e.g., (b) (4) and the MnB Bivalent (b) (4) 6 DP (e.g., (b) (4) are operated and controlled by a (b) (4). All equipment is operated in an automatic mode, when possible, by the validated (b) (4) which is also used for on-line, in-process data acquisition.

A separate (b) (4) is used to control and monitor the HVAC and refrigeration systems as to monitor the environmental conditions in production areas. Other production equipment may be partly computerized by (b) (4) or software (e.g., filling and inspection systems).

For the manufacturing processes, only qualified and validated computer systems are used, as applicable. Validation includes IQ/OQ or verification. Periodic reviews of the computer systems are performed to ensure the systems remain in a validated state.

**Reviewer's comment:** *Qualified computer systems are used during the manufacturing process, when possible, and to monitor and control the manufacturing areas. The information provided appears acceptable.*

#### Utilities

##### HVAC

##### Description

The (b) (4) manufacturing areas and (b) (4) are serviced by an HVAC system in an area adjacent to the suite. The HVAC system includes (b) (4) AHUs that recirculate air and the distributed ductwork.

The (b) (4) manufacturing areas are serviced by an HVAC system located in the (b) (4) building (b) (4). The HVAC system includes an arrangement of primary AHUs and several secondary AHUs.

Each (b) (4) AHU and the primary (b) (4) AHUs (b) (4)

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

(b) (4)

**Reviewer's comment:** The HVAC system serving the (b) (4) Manufacturing Building Appears has been qualified to maintain air quality in the production areas. The utilities appear acceptable.

*Environmental Monitoring*

Cleanrooms and manufacturing areas in the (b) (4) Manufacturing Building are classified per (b) (4) GMP Volume (b) (4) guidelines. The routine monitoring frequency and action levels are the following:

- Grade (b) (4)

(b) (4)

- Grade (b) (4)

(b) (4)

- Grade (b) (4)

(b) (4)

(b) (4)

- Grade <sup>(b) (4)</sup>

(b) (4)

**Reviewer's comment:** The applicant described the types of EM, sampling frequency and the action levels for classified areas. The EM program appears acceptable to detect potential contamination in production areas. The HVAC system and EM results from vaccine manufacturing areas at the facility were reviewed during the <sup>(b) (4)</sup> surveillance inspection.

(b) (4)

5 pages have been determined to be not releasable: (b)(4)

(b) (4)

### 3.2.R Regional Information (USA)

#### Combination Products

The (b) (4)-MnB PFS and MenABCWY vaccine are combination products. Pfizer takes a streamlined approach to comply with the current good manufacturing practice (GGMP) requirements with the overarching quality systems in accordance with the drug and biologics CGMPs and integration of the specific device Quality System Regulation (QSR) provisions that include Management Responsibility, Design Controls, Purchasing Controls, and Corrective and Preventive Actions (CAPAs). Note: Installation and Servicing are not applicable to the products. The applicant and license holder maintains responsibility and is the holder of information for the MenABCWY vaccine under the QSR.

**Reviewer's comment:** Pfizer provided summaries to explain how it complies with the device QSR provisions for Management Responsibility, Purchasing Controls, and CAPAs. The information provided appears acceptable.

In Sections 3.2.P.3.1 for the (b) (4) MnB and MenABCWY vaccine, Pfizer noted the CGMP requirements for the combination product applies at (b) (4) (b) (4) and (b) (4) respectively. This appears acceptable as (b) (4)



(b) (4) is the location of the manufacture of (b) (4)-MnB, which is filled into a PFS – a single entity combination product, and (b) (4) is the location of the manufacture of the MenABCWY vaccine, which is a vaccine kit – a co-packaged combination product.

*The design controls, including the risk analysis, are deferred to OVR.*

#### Comparability Protocols

(b) (4)

2 pages have been determined to be not releasable: (b)(4)