



BLA Device Review Memorandum – Prefilled Syringe (PFS)

Memo Date:	October 16, 2023
Device Reviewer:	Andrea Gray, PhD, CBER/ORO/DROP/RPB
To:	Chair and RPMs listed below
STN:	125770
Applicant:	Pfizer Ireland Pharmaceuticals c/o Pfizer Inc (US Agent)
Contact:	Malgorzata (Gosia) Mineo Director, Pfizer Global Regulatory Sciences – Vaccines 1 Pfizer Way 190/004/4405 Pearl River, NY 10965
Product Name:	Meningococcal Groups A, B, C, W and Y Vaccine (MenABCWY)
Product Description:	The MenABCWY vaccine carton consists of a single-dose of MenACWY-TT DP component (sterile lyophilized powder) in a 2 mL vial, a single dose of MnB Bivalent (b) (4) DP component (sterile liquid suspension) in a 1 mL prefilled syringe and a vial adapter.
Combination Product Information:	
Category (biologic-device, drug-device, drug-device-biologic):	Biologic-Device
Biologic Constituent(s):	Vaccines (MenACWY-TT, MnB Bivalent (b) (4))
Drug Constituent(s):	n/a
Device Constituent(s):	Prefilled syringe
Indication for Use:	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
Route of Administration:	Intramuscular injection
Review Team:	
RPM:	Brynn Hollingsworth (DVRPA), Maria Bagh (DVRPA), Moonsuk Choi (DVRPA), Maureen Demar (DMPQ)
Chair:	Michael Smith (DVRPA)
CMC:	Lunhua Liu (DBPAP), Kathryn Matthias (DBPAP), Lisa Parsons (DBPAP)
DMPQ:	Jared Greenleaf, Cheryl Hulme, Kathleen Jones, Miriam Ngundi
Consult(s) (name, affiliation, ICCR # and link):	

Engineering:	n/a
Human Factors:	none
Relevant Cross Reference(s):	DMF (b) (4), DMF (b) (4), DMF (b) (4) DMF (b) (4) DMF (b) (4) DMF (b) (4) BB-IND 017319, (b) (4) BLA 125549 510(k) (b) (4) 510(k) (b) (4)
Milestones:	
Filing Meeting:	December 5, 2023
Mid-Cycle Meeting (int):	April 5, 2023
Late Cycle Meeting (int):	June 28, 2023
Action Due Date:	October 20, 2023

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NOTE: Hover mouse over [blue underlined text](#) for additional information/instruction.

I. Executive Summary and Recommendations

Pfizer submitted a BLA for licensure of their Meningococcal Groups A, B, C, W and Y Vaccine (MenABCWY), which includes a single-dose of lyophilized MenACWY-TT drug product (DP) component in a 2 mL Type (b) (4) glass vial, a non-graduated 1 mL Type (b) (4) glass pre-filled syringe (PFS) containing a single-dose suspension of MnB Bivalent (b) (4) DP component, and a (b) (4) vial adapter. This scope of this review memo includes device evaluation of the pre-filled syringe. Information cross referenced to master files is documented in separate review memos. Based on the information provided in the application and cross-referenced master files, as well as additional information submitted interactively, I recommend that the BLA can be approved from a device/combination product perspective.

Filing Recommendation Date: n/a

- ☒ CBER Device Reviewer did not provide a Filing Recommendation
- ☐ Device Constituent Parts of the Combination Product are acceptable for Filing
- ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests
- ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing

Mid-Cycle Recommendation Date: April 5, 2023

- ☐ CBER Device Reviewer did not provide a Mid-Cycle Recommendation
- ☒ CBER Device Reviewer has no approvability issues at this time
- ☒ CBER Device Reviewer has additional Information Requests
- ☐ CBER Device Reviewer has Major Deficiencies that may present an approvability issue

Final Recommendation Date: October 10, 2023

- ☒ CBER Device Reviewer Constituent Parts of the Combination Product are Approvable
- ☐ CBER Device Reviewer Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments
- ☐ CBER Device Reviewer Constituent Parts of the Combination Product are Not Approvable

Digital Signatures:

Reviewer:

Branch Chief:

II. Comment Summary

A. Comments to the Review Team

- ☒ CBER Device Reviewer does not have any further comments to convey to the review team.
☐ CBER Device Reviewer has the following comments to convey to the review team:

B. Complete Response Deficiencies

- ☒ CBER Device Reviewer does not have any outstanding deficiencies.
☐ The following outstanding unresolved information requests should be communicated to the Applicant as part of the CR Letter:

C. Recommended Post-Market Commitments/Requirements

- ☒ CBER Device Reviewer does not have Post-Market Commitments or Requirements
☐ CBER Device Reviewer has the following recommendations for Post-Market Commitments or Requirements:

III. Relevant Prior Interactions

Pfizer provided a tabulated record of previous communications with the Agency regarding this product in Modules 1.6.3 and 1.12.4. I (CBER device reviewer) became involved with review of this product after submission of the BLA (email dated November 18, 2022, and January 19, 2023) and was not part of any communications regarding this file prior to that. I became the device consult reviewer for the BLA, added as a review team member in RMS-BLA on January 19, 2023.

IV. Materials Reviewed

Sequence	Amd (STN 2 nd Level)	Details
0001*	0	Original submission
0033	24	Response to device information request

*All information comes from Sequence 0001 unless otherwise stated.

Pfizer cross references the following master files to support the PFS information in the BLA:

Table 3.2.P.2.4-2. List of Component DMF References

Component	DMF Reference
1 mL (b) (4) Type (b) (4) borosilicate glass with (b) (4) tip cap assembly that includes a Luer lock adapter, a rigid cap, and a tip cap. Syringe barrel is (b) (4). Tip cap is composed of gray (b) (4) elastomer (b) (4).	(b) (4) – Syringe, plunger rod – Syringe tip cap elastomer
1 mL (b) (4) Type (b) (4) borosilicate glass with (b) (4) tip cap assembly that includes a Luer lock adapter, a rigid cap, and a tip cap. Syringe barrel is (b) (4). Tip cap is composed of gray (b) (4) blend rubber).	(b) (4) – Syringe – Syringe tip cap elastomer
1-3 mL plunger stopper composed of gray (b) (4) elastomer (chlorobutyl rubber). Plunger stopper is (b) (4).	(b) (4) – Plunger stopper – Plunger stopper

Table 1.4.2-1. DMF Letters of Authorization

DMF Holder	DMF Reference	DMF Subject	Reference Information
Pre-filled syringe components			
(b) (4)	(b) (4) – Syringe, plunger rod	(b) (4) Glass Prefillable Syringe (PFS)	(b) (4) 1 mL (b) (4) glass syringe with plastic rigid tip cap (b) (4) Luer lock connection
	(b) (4) – Plunger stopper	(b) (4) Glass Prefillable Syringe (PFS)	(b) (4) polypropylene plunger rod
(b) (4)	(b) (4) – Syringe	Primary Packaging Material Syringes as Manufactured in (b) (4)	(b) (4) 1 mL glass syringe with (b) (4) rigid cap Luer lock connection
(b) (4)	(b) (4) – Plunger stopper	Elastomeric Formulations, Coatings and Films	1-3 mL plunger stopper composed of gray (b) (4) elastomer
	(b) (4) – Syringe tip cap elastomer		Syringe tip cap composed of gray (b) (4) elastomer

Letters of Authorization (LOAs) are provided in Module 1.4.2 and state the master files are current. LOA for DMF (b) (4) (b) (4) syringe barrel) further identifies the following information:

Applicant Company: Pfizer Ireland Pharmaceuticals Operations Support Group Building.

Applicant Drug: MenABCWY (Penta)

Applicant Filing: BLA

Catalogue Number	Component Description	eCTD Document ID(s)	Manufacturing / Depyrogenation Site(s)	Sterilization Site(s)*
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(b) (4)

Reviewer Comment: Although these DMFs are referenced, Pfizer did not list what specific information they are cross referencing to the DMFs (see IR#1.1 below).

Information Request #1.1	Date Sent: June 30, 2023	Date/Sequence Received: July 14, 2023 / 0033
IR Comment	Table 3.2.P.2.4-2 [MnB Bivalent (b) (4)] lists the master files you are cross referencing to support the syringe components of your product. For each referenced master file, please	

	indicate the specific information you are relying on the master file for (e.g., verification of certain design aspects per (b) (4) biocompatibility, etc.). Please note you may need to communicate with the master file holder to confirm that certain pieces of information that you are relying on are included in the master file.						
Sponsor Response	<p>The master files referenced in Table 3.2.P.2.4-2 of the previously submitted Section 3.2.P.2.4 Container Closure System (MnB Bivalent (b) (4) incorrectly referenced DMF (b) (4) pertaining to the 1-3 mL plunger stopper and syringe tip cap composed of gray (b) (4) elastomer material. Letters of Authorization to the correct reference, DMF (b) (4), are provided for both the syringe tip cap elastomer and the plunger stopper. Letters of Authorization to the incorrect DMF (b) (4) have been removed.</p> <p>The table below lists the master files being referenced for biocompatibility information related to the components of the syringe. The table details the component referenced and the DMF section containing proprietary supplier design information applicable to the referenced components.</p> <table><tr><th>Component</th><th>DMF Information Referenced</th><th>Location of Information in DMF</th></tr><tr><td colspan="3">(b) (4)</td></tr></table>	Component	DMF Information Referenced	Location of Information in DMF	(b) (4)		
Component	DMF Information Referenced	Location of Information in DMF					
(b) (4)							
Reviewer Comments	Clarification is sufficient. Review of the referenced master files is primarily limited to biocompatibility. Notably, the biocompatibility information in MF (b) (4) is of limited utility to support the BLA, as it provides information on the elastomer rather than the final finished plunger stopper.						

V. Information Request Log

IR#	Date Sent	Requested Info	Date of Response	Sequence	Amd (STN 3 rd Level)
1	June 30, 2023	1. Identification of what information is cross referenced to master files 2. Additional information on (b) (4) (b) (4) test methods 3. Additional information in consensus standard used to evaluate the luer lock adaptor performance 4. Additional information regarding the plunger rods and finger grips 5. Stability data for (b) (4) months) and evaluation of (b) (4) stability program 6. Additional information on functionality test performed on incoming syringe lots and additional information on (b) (4) (b) (4)	July 14, 2023	0033	24

VI. Product Description

A. Combination Product

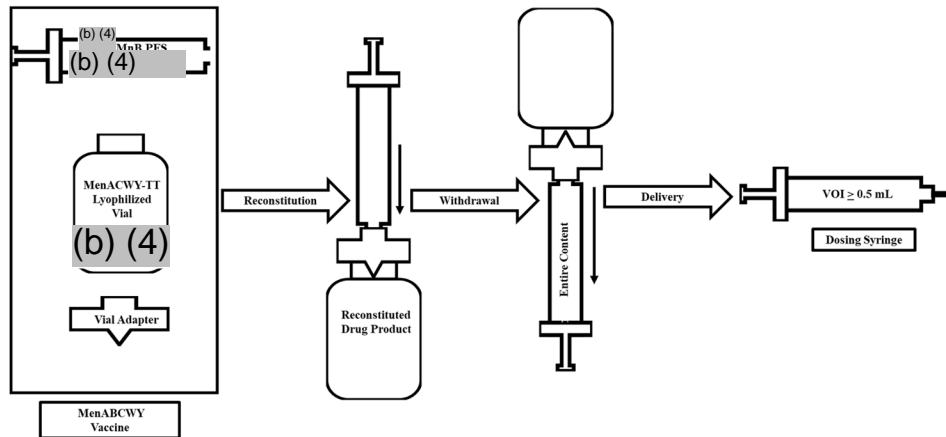
Per Module 2.2, "Meningococcal groups A, B, C, W and Y vaccine is a suspension for injection following reconstitution of a single-dose vial of lyophilized MenACWY-TT vaccine component with the accompanying prefilled syringe of MenB-fHbp suspension vaccine component. A single dose after reconstitution is 0.5 mL... The proposed indication is active immunization of individuals 10 through 25 years of age to prevent invasive disease caused by Neisseria meningitidis groups A, B, C, W, and Y... It is recommended to administer the second dose at least 6 months after the first dose."

The kit contains:

- Lyophilized MenACWY-TT DP component in a 2 mL Type (b) (4) glass vial
- Non-graduated 1 mL Type (b) (4) glass pre-filled syringe (PFS) containing a single-dose suspension of MnB Bivalent (b) (4) DP component
- 13 mm vial adapter

Per Module 2.3.1, "The lyophilized MenACWY-TT DP component is reconstituted with the MnB Bivalent (b) (4) DP component using the supplied vial adapter. After reconstitution, the content of the vial is withdrawn into the same syringe via the vial adapter... The vial adapter is detached from the syringe and a needle will be affixed to the syringe for IM injection. The target dose of the MenABCWY vaccine is (b) (4) 0.5 mL."

Figure 3.2.P.2.2-1. Preparation of MenABCWY Vaccine Dosing Solution



Notably, “he MnB Bivalent (b)(4) DP component is based on the Trumenba vaccine, which was approved in the US on October 29, 2014... (STN: BLA 125549)...” The presentation in the MenABCWY vaccine has a (b)(4) (b)(4) than Trumenba to ensure that a target dose of the MenABCWY vaccine can be administered.” Subsequently, the MnB Bivalent (b)(4) drug product component is also referred to as (b)(4) MnB (b)(4)-MnB).

B. MnB Bivalent (b)(4) DP

The contents of the syringe are below (Module 3.2.P.1.2 [MnB Bivalent (b)(4)]):

Table 3.2.P.1-1. Composition of MnB bivalent (b)(4) Drug Product Component

Ingredient	Grade/Quality Standard	Function	Amount /Syringe	Amount /Dose ^a
MnB (b)(4) subfamily A	(b)(4)	(b)(4)	(b)(4)	(b)(4)
MnB (b)(4) subfamily B				
(b)(4)				
(b)(4)				
Polysorbate 80				
(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
(b)(4)				

a. Amount/Dose is the contribution to the final administered dose of the combined MenABCWY vaccine from the syringe. The volume of the administered dose is 0.5 mL.

b. (b)(4) or (b)(4) are used as (b)(4) as needed

Physical properties of the MnB Bivalent (b)(4) are provided in Module 3.2.P.2.2 Drug Product:

Table 3.2.P.2.2-6. Representative Physical Properties of MnB Bivalent (b)(4) Drug Product Component (Measurement from Trumenba Vaccine)

(b)(4)

C. Syringe

The MnB Bivalent (b)(4) DP component is supplied as a single dose suspension in a non-graduated 1 mL Type (b)(4) glass pre-filled syringe (PFS). Notably, per 3.2.P.2.4.1, “The **components of the (b)(4)-MnB PFS are identical to those of the commercial Trumenba vaccine**, therefore, (b)(4)-MnB drug product component development was based on the development of the commercial Trumenba vaccine.”

General Description

Components (e.g., barrel, plunger rod, plunger stopper, etc.)	(b) (4) syringe barrel, plastic rigid tip cap (PRTC) tip cap assembly (Luer lock adapter (LLA), tip cap cover), plunger stopper, plunger rods (b) (4) syringe barrel, (b) (4) rigid cap (b) (4) tip cap assembly (Luer lock adapter (LLA), tip cap cover) (b) (4) plunger stopper (b) (4) tip cap (in the PRTC and (b) (4) tip cap assemblies supplied by (b) (4)) (b) (4) finger grip	
Connection type (e.g., luer, slip tip, staked needle)	Luer	
Intended Connector (e.g., vial adaptor, needle, needless connector, etc.)	Vial adaptor (supplied), hypodermic needle (not supplied)	
Materials of construction (including (b) (4))	(b) (4) Barrel Subassembly Barrel: Type (b) (4) Borosilicate glass (b) (4) (b) (4) LLA: polycarbonate Rigid Cap: polypropylene Tip Cap: gray (b) (4) elastomer (synthetic isoprene/bromobutyl blend rubber)	(b) (4) Barrel Subassembly Barrel: Type (b) (4) Borosilicate glass (b) (4) (b) (4) LLA: polycarbonate Rigid Cap: polypropylene Tip Cap: gray (b) (4) elastomer (synthetic isoprene/bromobutyl blend rubber)
	Plunger stopper: gray (b) (4) elastomer (chlorobutyl rubber) (b) (4)	
	Plunger Rod: polypropylene	
	Finger grip: polypropylene	

Dimensions	(b) (4)	
Syringe Volume	1 mL	
Fill Volume	(b) (4) (an (b) (4) to ensure a nominal extractable volume of (b) (4)	
Number of Doses per syringe	Volume sufficient to reconstitute one (1) dose of the MenACWY-TT DP component	
Injection Site	Preferably into the deltoid muscle of the upper arm	
Injection tissue and depth of injection	Intramuscular; injection depth necessary for intramuscular administration of vaccines is common knowledge in healthcare community	
Type of Use (e.g., single use, disposable, reusable, other)	Single use	
Storage conditions and proposed expiry (i.e., shelf life)	2°C to 8°C, 24 months	
User and Use Environment		
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	Healthcare professional (HCP)	

Environments of use (e.g., home, clinic)	Clinic
Additional Aspects	
Hypodermic Needle: length, gauge, and configuration of the tip.	Not provided with product; needle specifications necessary for intramuscular injections of vaccines are common knowledge in healthcare community
Markings (graduated scale, position of scale, length of scale, numbering of scale, and legibility criteria (for insulin syringes)).	No graduations or markings
Reuse Durability (for reusable piston syringes): number of times the device can be sterilized and still meet specifications (using sterilization method indicated in the labeling).	n/a
Safety Features (e.g., Needle safety component/device)	n/a
Automated Functions	n/a
Sterilization method	(b) (4)

D. Vial Adaptor

Description	Individually packaged, sterile, commercially available
Regulatory Status (e.g., 510(k) number)	(b) (4) (b) (4)
Connection type (e.g., luer, slip tip)	Luer connection to syringe, spike connection to vial
Materials of construction	Polycarbonate

VII. Manufacturing

A. Manufacturers

Syringe Component Suppliers

Table 3.2.P.7-2. ^{(b) (4)} Syringe Manufacturing and Sterilization Sites

(b) (4)

Table 3.2.P.7-3. ^{(b) (4)} Syringe Manufacturing and Sterilization Sites

(b) (4)

Table 3.2.P.7-8. Plunger Stopper Manufacturing, Processing, and Sterilization Sites

(b) (4)

MnB Bivalent (b) (4) *PFS*

Table 3.2.P.3.1-1. Sites, Responsibilities, and 21 CFR Part 4 Requirements for
AlPO₄ Suspension and (b) (4)-MnB

(b) (4)

MenABCWY Kit

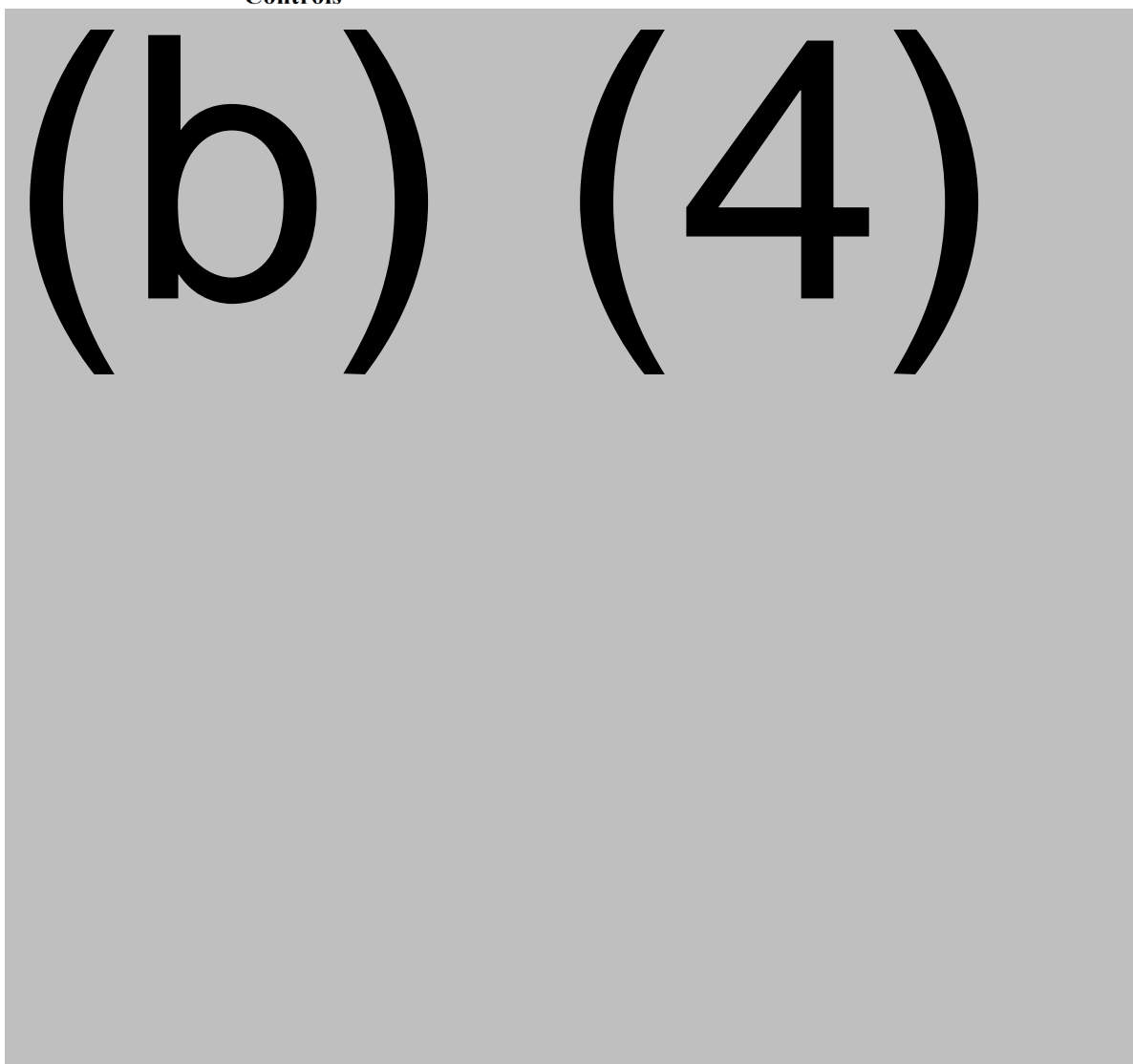
Table 3.2.P.3.1-1. Sites, Responsibilities, and 21 CFR Part 4 Requirements for MenABCWY Drug Product

(b) (4)

B. Manufacturing Process

Manufacturing processes for the (b) (4)-MnB PFS and the final kit (MenABCWY) are described in the respective Modules 3.2.P.3.3.

Figure 3.2.P.3.3-1. Description of Overall Manufacturing Process and Process Controls



Reviewer Comment: Overall manufacturing process and facilities reviews are deferred to CMC and DMPQ.

(b) (4)

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

Reviewer Comment: See [Section XI](#) of this memo for review of essential performance requirement (EPR) control strategy.

MnB Bivalent (b) (4)PFS

Table 3.2.P.5.1-1. MnB Bivalent (b) (4) Drug Product Component Specifications for Release and Stability Testing

Quality Attribute	Method	Acceptance Criteria	
		Release	Stability
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Appearance	Visual	Homogeneous white suspension	Homogeneous white suspension
Container Closure Integrity	(b) (4)	N/A ^a	Pass
(b) (4)			
Polysorbate 80 (b) (4)	(b) (4)		
(b) (4)			
Sterility	(b) (4)	Meets the requirements of the test. No growth observed	Meets the requirements of the test. No growth observed ^b
(b) (4)			

Module 3.2.P.3.4 describes the following method qualification

(b) (4)

(b) (4)

MenABCWY Kit

Table 3.2.P.5.1-1. MenABCWY Drug Product Specification

Quality Attribute	Analytical Procedure	Acceptance Criteria	
		Release	Stability
Appearance (After Reconstitution)	Visual Inspection	Homogeneous white suspension	Homogeneous white suspension
Protein (Total), µg/mL each subfamily (A and B)	(b) (4)		
(b) (4)	(b) (4)		
Volume of Injection, mL	(b) (4)	(b) (4) 0.5	(b) (4) 0.5

Abbreviations: (b) (4)

(b) (4)

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

(b) (4)

Table 3.2.P.5.4-2. Batch Analyses for MenABCWY Drug Product for Clinical Use

Lot Number			DA4348/2-DK9946
Lot Designation			Phase 3 Clinical
Quality Attribute	Analytical Procedure	Acceptance Criteria	Results
Appearance (After Reconstitution)	Visual	Homogeneous white suspension	Homogeneous white suspension
(b) (4)			
Volume of Injection	(b) (4)	(b) (4) 0.5 mL	0.5

(b) (4)

(b) (4)

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



VIII. Design Verification

The following table from in Module 3.2.P.2.2 Drug Product [MenABCWY] for

Table 3.2.P.2.2-3. Volume Definitions for MenABCWY Vaccine

Terminology	Fill Volume	Volume of Reconstitution	Extractable Volume	Volume of Injection
Description	Target volume (b) (4) (b) (4) MnB PFS	Target volume (b) (4) MnB PFS into lyophilized drug product vial through vial adapter	QC release test of volume expelled from (b) (4) MnB PFS	Entire content from reconstituted drug product vial (MenABCWY) delivered using dosing syringe
Volume	(b) (4)	(b) (4)	(b) (4)	(b) (4) 0.5 mL

Abbreviations: PFS = Prefilled Syringe; QC = Quality Control

The following table was provided in Module 3.2.P.2.4 Container Closure [MnB Bivalent (b) (4) for the (b) (4) MenB **PFS alone**. The information is reviewed in the subsequent reviewer-generated table.

Table 3.2.P.2.4-14. Summary of Product Performance

Requirement Description	Acceptance Criteria	Designation	Evidence	Control of Requirement
The combination product shall comply with (b) (4) concerning the extractable volume	Minimum extractable volume of (b) (4)	EPR	Verified – Refer to Section 3.2.P.2.2 Drug Product [MnB Bivalent (b) (4)]	<p>Extractable volume is determined by fill volume and plunger stopper placement. A (b) (4) check is used as an IPC test to ensure the PFS are within the target fill volume. Plunger stopper placement is also monitored by an IPC test to ensure the stopper is placed within the target range. Reference Section 3.2.P.2.3 Control Strategy Summary [MnB Bivalent (b) (4)], Section 3.2.P.3.3 Filling [MnB Bivalent (b) (4)] and Section 3.2.P.3.4 Filling [MnB Bivalent (b) (4)]. Extractable volume has been assessed after shipping (Section 3.2.P.3.5 Shipping Validation [MenABCWY]) and will also be tested on commercial release (refer to Section 3.2.P.5.1 Specifications [MnB Bivalent (b) (4)]).</p> <p>Extractable volume is not considered stability indicating as the container closure system remains integral over the shelf life of the product. The CCI test is scheduled for long term stability to ensure the integrity of the container (refer to Section 3.2.P.8.1 Stability Summary and Conclusion [MnB Bivalent (b) (4)] and by extrapolation, that the extractable volume does not change over time at the intended storage conditions.</p> <p>Given the data collected throughout development and incoming and manufacturing controls in place, extractable volume is deemed controlled and does not need to be tested on commercial lot release or as part of the formal stability studies captured in Section 3.2.P.8.1 Stability Summary and Conclusion [MnB Bivalent (b) (4)].</p>

During dose preparation and delivery, the force required by the user to start and sustain the plunger stopper movement shall be less than or equal to (b) (4)	(b) (4) when delivered at a rate of (b) (4) (b) (4) regular wall needle	EPR	Verified – Refer to Section 3.2.P.2.4.5.1.1. (b) (4) remains NMT (b) (4) throughout the proposed shelf life of the product.	(b) (4) has been extensively characterized through design verification, transportation studies, clinical release testing, and over stability (refer to Section 3.2.P.2.4.5.1.1). All results have been within the specified acceptance criteria. Supplier certificates of analysis for both the syringe and plunger stopper ensure consistent product is received. Sufficient data has been collected to demonstrate this attribute is well controlled and does not need to be tested routinely.
The syringe shall have a (b) (4) Luer conical lock fitting with internal threaded collar that meets the functional (b) (4) requirements of (b) (4)	The syringe has a (b) (4) Luer conical lock fitting with internal threaded collar that meets the (b) (4) requirements of (b) (4) (b) (4) (b) (4)	Other-Performance / Compatibility	Verified – (b) (4) testing according to (b) (4) (b) (4) has been performed on the syringe assembled by the supplier. In addition, (b) (4) testing according to (b) (4) (b) (4) was performed on filled (b) (4) MnB PFS.	The syringe supplier certify compliance to (b) (4) (b) (4) with each batch of components received. (b) (4) testing according to (b) (4) (b) (4) was also performed on filled (b) (4) MnB PFS as part of Design Verification. Sufficient data has been collected to demonstrate this attribute is well controlled and does not need to be tested routinely.
The (b) (4) MnB prefilled syringe allows for secure connectivity, delivery of contents, and container closure safety and performance.	Compliance to applicable sections of (b) (4) (b) (4) based on design and administration	Other-Performance	Verified Verified	Section (b) (4) applies for usability, risk management, user needs and design inputs. Reference Section 3.2.P.2.4.9 for Risk Management, Section 3.2.P.2.4.8 for validation of User Needs, and Section 3.2.P.2.4.5.1 for verification of select Design Inputs. Section 5 applies for definition of critical dimensions for connectivity and interface between the syringe and the device accessories (vial adapter), as well as plunger stopper position. Both the syringe and vial adapter are certified to comply with the functional (b) (4) requirements of applicable (b) (4) standards. (b) (4) testing according to (b) (4) was also

			Verified	<p>performed on filled (b) (4) MnB PFS as part of Design Verification. Reference Section 3.2.P.2.4.6 for plunger stopper position.</p> <p>Section 6 applies for (b) (4) connectivity, (b) (4) beyond plunger. Reference Section 3.2.P.2.4.5.1.1 for (b) (4). Both the syringe and vial adapter are certified to comply with the functional (b) (4) requirements of applicable (b) (4) Luer standards. (b) (4) (b) (4) testing according to (b) (4) (b) (4) was also performed on filled (b) (4) MnB PFS as part of Design Verification. Representative MnB syringes using (b) (4) syringe barrels were found to conform to the plunger (b) (4) requirements of (b) (4) (b) (4).</p>
			Verified	<p>Section 7 applies for leachable, extractables from drug-container interaction; biocompatibility; container closure integrity and sterility; deliverable volume. Reference Section 3.2.P.2.4.3.4 for Extractables, Section 3.2.P.2.4.3.5 for Leachables, Section 3.2.P.2.4.3.2 for Biocompatibility, Section 3.2.P.8.1 Stability Summary and Conclusions [MnB Bivalent (b) (4)] for Stability (container closure integrity and sterility), Section 3.2.P.2.4.5.1 for deliverable volume.</p>

*Only applicable sections listed for (b) (4)

The following table was provided in Module 3.2.P.2.4 Container Closure [MenABCWY] for the **overall final kit**. The information is reviewed in the subsequent reviewer-generated table.

Table 3.2.P.2.4-2. Summary of Product Performance

Requirement Description	Acceptance Criteria	Designation	Evidence	Control of Requirement
The combination product shall comply with (b) (4) concerning the volume of injection	Minimum volume of injection of 0.5 mL	EPR	<p>Verified – Refer to Section 3.2.P.2.2 Drug Product [MenABCWY]. When the (b) (4) MnB PFS is used with the vial adapter, sufficient volume is extracted that can reconstitute the MenACWY-TT drug product component and then be withdrawn and delivered as (b) (4) 0.5 mL of reconstituted MenABCWY drug product when using a needle suitable for intramuscular injection.</p>	<p>Volume of injection has been assessed through development studies and design verification, including measurement of hold up volume within the vial adapter, PFS and vial. Incoming material controls, including confirmation of syringe conformance to (b) (4) (b) (4) are in place. Studies have been conducted demonstrating that if extractable volume is maintained, volume of injection will be within the acceptance criteria (refer to Section 3.2.P.2.2 Drug Product [MenABCWY]).</p> <p>Volume of injection has been assessed after shipping (Section 3.2.P.3.5 Shipping Validation [MenABCWY]) and is included as part of the MenABCWY release specifications (refer to Section 3.2.P.5.1 Specification(s) [MenABCWY]). Volume of injection is not considered stability indicating as the container closure system remains integral over the shelf life of the product. The CCI test is scheduled for long term stability to ensure the integrity of the container (refer to Section 3.2.P.8.1 Stability Summary and Conclusion [MnB Bivalent (b) (4)] and by extrapolation, that the volume of injection does not change over time at the intended storage conditions.</p>

During dose preparation and delivery, the force required by the user to start and sustain the plunger stopper movement shall be less than or equal to (b) (4)	(b) (4) when delivered at a rate of (b) (4) regular wall needle suitable for intramuscular injection (for delivery) or through a vial adapter into the vial (for dose preparation).	EPR	Verified – Refer to Section 3.2.P.2.4.2.2. (b) (4) remains (b) (4) throughout the proposed shelf life of the product	(b) (4) has been extensively characterized through design verification, transportation studies, clinical release testing, and over stability (refer to Section 3.2.P.2.4.2.2). All results have been within the specified acceptance criteria. Incoming controls are in place to assess both the syringe and plunger stopper to ensure consistent product is received. Sufficient data has been collected to demonstrate this attribute is well controlled and does not need to be tested routinely.
The kit shall include a sterile commercially available vial adapter compatible with the PFS	The kit shall include a sterile individually packaged vial adapter with a (b) (4) Luer conical lock fitting with lugs at right angle to axis that is certified to be meet the functional (b) (4) requirements of (b) (4) or (b) (4) (b) (4)	Other – Compatibility	Verified - The vial adapter is an individually packaged, sterile, commercially available medical device purchased from (b) (4) (b) (4) that is specified to comply with the functional (b) (4) requirements of (b) (4) (b) (4) or (b) (4) (b) (4) respectively	The vial adapter supplier certifies conformance to (b) (4) (b) (4) or (b) (4) (b) (4)
The vial adapter shall be selected for use with a 13 mm finish vial with a standard crimp seal	The vial adapter is to be compatible with a 13 mm finish DP vial with a standard crimp seal	Other – Compatibility	Verified - The vial adapter is an individually packaged, sterile, commercially available medical device purchased from (b) (4) (b) (4) that is specified for use with a 13 mm finish vial	The vial adapter supplier certifies compatibility with a 13 mm finish vial.

<p>The PFS Luer lock adapter shall not become dislodged during dose preparation or administration</p>	<p>The PFS is capable of undergoing the entire dose preparation and administration process without dislodging the Luer lock adapter.</p>	<p>Other - Performance</p>	<p>Verified – (b) (4) testing per (b) (4) Clause (b) (4) has been performed on filled (b) (4) MnB PFS.</p>	<p>The syringe supplier certify compliance to (b) (4) (b) (4) with each batch of components received. (b) (4) testing according to (b) (4) (b) (4) was also performed on filled (b) (4) MnB PFS as part of Design Verification. During this (b) (4) the (b) (4) (b) (4) according to (b) (4) (b) (4)</p> <p>The vial adapter was chosen to interface with the PFS Luer lock adapter and is also certified compliant to (b) (4) (b) (4) by the supplier.</p>
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4 pages have been determined to be not releasable: (b)(4)

(b) (4)

Information Request #1.2	Date Sent: June 30, 2023	Date/Sequence Received: July 14, 2023 / 0033
IR Comment	You provided information regarding essential performance requirements (EPR) verification in Module 3.2.P.2.4 [MnB Bivalent (b) (4)] and Module 3.2.P.2.4 [MenABCWY]. You provided verification data for (b) (4) (b) (4) for the MnB Bivalent (b) (4) PFS and final combination product representing the full dose preparation and administration procedure. However, you did not provide adequate description of test methods. Please provide a brief description of the test methods including any consensus standard(s) utilized. If you cite general use of a consensus standard (e.g., (b) (4) (b) (4) please provide the full citation of the standard, including the version and publication year, and information regarding the extent to which the standard was followed, including deviations from the standard.	
Sponsor Response	Methods used to generate (b) (4) data presented in previously submitted Section 3.2.P.2.4 Container Closure System [MnB Bivalent (b) (4)] and Section 3.2.P.2.4 Container Closure System [MenABCWY] were performed in line with the method listed in (b) (4) (b) (4) (referred to as “the standard”) with minor deviations to the standard that do not impact the validity of the results. Deviations from the standard are summarized in Table 1 and are associated with sample configuration, sample preparation and the reporting of (b) (4) of a filled syringe versus the (b) (4) of an empty syringe. Table 1. Summary of Deviations to (b) (4)(b) (4)	
<div>(b) (4)</div>		

(b) (4)

SUPPORTING DOCUMENTATION

New or Replaced Supporting Documentation

[Section 3.2.P.2.4 Container Closure System \[MnB Bivalent \(b\) \(4\)\]](#), Replaced, sequence 0001 (updated due to the [Response to Query 1](#))

[Section 3.2.P.2.4 Container Closure System \[MenABCWY\]](#), Replaced, sequence 0001 (updated due to the [Response to Query 5](#))

Previously Submitted Supporting Documentation

None

**Reviewer
Comments**

Response is acceptable.

(b) (4)

Information Request #1.3	Date Sent: June 30, 2023	Date/Sequence Received: July 14, 2023 / 0033
IR Comment	You provided information regarding device performance verification (non-EPR) in Modules 3.2.P.2.4 [MnB Bivalent (b) (4)] and Module 3.2.P.2.4 [MenABCWY], including (b) (4) testing per (b) (4) (b) (4) to demonstrate the luer connection does not (b) (4) and that the LLA does not become dislodged during dose preparation or administration. Please provide additional information on your use of (b) (4) (b) (4) including the full citation of the standard (including the version and publication year) and information regarding the extent to which the standard was followed, including deviations from the standard.	
Sponsor Response	(b) (4) testing was performed per (b) (4) (b) (4) on the MnB Bivalent (b) (4) Prefilled Syringe (PFS) and the final MenABCWY Vaccine PFS. Acceptance criteria for this attribute is specified as "Luer connectors evaluated for (b) (4) performance with the (b) (4) test method shall show no signs of (b) (4) sufficient to (b) (4) of (b) (4) to (b) (4) while being subjected to an (b) (4) of between (b) (4) and (b) (4) ." There were no exceptions/deviations in testing. Connectivity requirements were aligned with criteria specified in (b) (4) (b) (4) using the associated test methods found in (b) (4) (b) (4) . There were no exceptions/deviations in testing from the standard requirements.	
Reviewer Comments	<i>Response is acceptable.</i>	



IX. Biocompatibility

NOTE: Extractables/leachables/toxicological risk assessment deferred to CMC review.

A. Syringe

Contact Classification (as defined by Pfizer):

- Syringe Barrel with Tip Cap Assembly: Externally Communicating Device, Blood Path, Indirect
- Plunger Stopper: Externally Communicating Device, Blood Path, Indirect
- Plunger Rod: Surface contact with intact skin
- Finger Grip: Surface contact with intact skin

Reviewer Comment: *Contact duration is somewhat irrelevant for the product-contacting components of a PFS (syringe barrel lumen, rubber tip cap, plunger stopper), as the indirect contact is via the PFS contents, which may be in contact with the syringe fluid path for an extended time, during storage prior to use. Thus, extractables/leachables testing and subsequent toxicological risk assessment is typically necessary to determine biological reactivity risk of the syringe materials, as with other non-device container closures.*

Module 3.2.P.2.4 Container Closure states “The plunger stopper and tip cap rubber insert elastomers of the container closure system comply with the biological activity requirements specified in (b) (4) ... As part of risk management and design verification, the compliance of the product components to (b) (4) biocompatibility requirements were evaluated and certified by the component suppliers. The data sits within the supplier DMFs...”

Reviewer Comment: (b) (4) “Elastomeric Closure for Injections”, Section 4.1 “Biological Reactivity” states “Elastomeric components (Type (b) (4) and Type (b) (4)) meet the requirements of Biological Reactivity Tests, (b) (4) (b) (4) If components do not meet the requirements of (b) (4) they can be subjected to (b) (4) testing set forth in Biological Reactivity Tests, (b) (4) (b) (4) Systemic Injection Test and (b) (4) Intracutaneous Test. Components that meet the requirements of (b) (4) are not required to undergo (b) (4) testing.” Therefore

Regarding the plunger rod, Pfizer states (b) (4) has shown the plunger rod fulfills the biological requirements of (b) (4) for Cytotoxicity, Sensitization, Irritation.” Regarding the finger grips, Pfizer states “(b) (4) have shown the finger grip fulfills the biological requirements of (b) (4) for Cytotoxicity, Sensitization, Irritation.”

Component	Endpoint (per Module 3.2.P.2.4)	X-ref to MF?	Reviewer Comment
Syringe Barrel with Tip Cap Assembly	Cytotoxicity	<input checked="" type="checkbox"/>	Refer to review memos for DMF (b) (4) and DMF (b) (4)
	Sensitization	<input checked="" type="checkbox"/>	
	Irritation	<input checked="" type="checkbox"/>	
	Acute systemic toxicity	<input checked="" type="checkbox"/>	
	Hemocompatibility	<input checked="" type="checkbox"/>	
	Material mediated pyrogenicity	<input checked="" type="checkbox"/>	
Plunger stopper	Cytotoxicity	<input checked="" type="checkbox"/>	Refer to review memos for DMF (b) (4) and MF (b) (4) See also Reviewer Comment above regarding (b) (4)
Plunger Rod	Cytotoxicity	<input checked="" type="checkbox"/>	These components are non-patient/product contacting. They are potentially HPC-contacting, but the contact duration is transient. Statement of certification from the manufacturers is sufficient.
	Sensitization	<input checked="" type="checkbox"/>	
	Irritation	<input checked="" type="checkbox"/>	
Finger Grip	Cytotoxicity	<input checked="" type="checkbox"/>	
	Sensitization	<input checked="" type="checkbox"/>	
	Irritation	<input checked="" type="checkbox"/>	

Review Comment: As indicated above and in **IR#1.1** (see [Section IV](#) of this memo), biocompatibility is referenced to the DMFs. Refer to the review memos for DMF (b) (4) (b) (4) syringe), DMF (b) (4) (b) (4) syringe), and MF (b) (4) (tip cap and plunger stopper elastomer formulations). The information provided in the (b) (4) DMF (b) (4) is adequate from a device perspective. Deficiencies were identified in the biocompatibility information in the (b) (4) submission. However, these deficiencies do not rise to CR-level safety concerns for the following reasons:

- The (b) (4) DMF (b) (4) deficiencies primarily concern missing information on methodology in the test reports. None of the provided reports stated findings of adverse biocompatibility findings. Biocompatibility tests from a device perspective (i.e., for the endpoints lists above) is not historically reviewed to this detail for PFS. The available reports were reviewed in detail in this instance for due diligence, to ensure no glaring biocompatibility issues.
- As PFS are both devices and container closure, review considerations are a balance of device perspective and container closure perspectives. Table 2 of the FDA guidance “Container Closure Systems for Packaging Human Drugs and Biologics”, “USP Biological Reactivity Test data and possibly extraction/toxicological evaluation” are typically provided to demonstrate safety of the container closure materials. The container closure guidance (1999) states “For many injectable and ophthalmic drug products (see sections III.E and III.F), data from the USP Biological Reactivity Tests and USP Elastomeric Closures for Injections tests will typically be considered sufficient evidence of material safety.” As stated above, extractables/leachables/toxicological risk assessment is deferred to CMC review. The CMC reviewer found the extractables/leachables/toxicological risk assessment information to be acceptable.
- The COAs for (b) (4) syringe barrels and tip cap elastomers state the materials meet the requirements of corresponding (b) (4) chapters (i.e., (b) (4) (b) (4) Containers – Glass, (b) (4) (b) (4) Elastomeric Closure for Injections). The (b) (4) COAs for the syringes and plunger stoppers also cite conformance to (b) (4).
- These PFS have extensive historic use and do not include novel materials or uses. The syringe components are already used in the US approved TRUMENBA (BLA 125549, see [Section VI.A](#) of this memo) as well as the recently approved ABRYSVO (BLA 125769).

B. Vial Adaptor

Contact Classification: External Communicating Device with Circulating Blood/Tissue contact (indirect) for Limited Duration (≤24 hours)

510(k) Number(s):	(b) (4) (b) (4)
Is contact classification of proposed device consistent with cleared 510(k)? If not, please evaluate the following:	yes
Are there additional biocompatibility endpoints that should be evaluated?	n/a

X. Sterilization

NOTE: Sterility and endotoxin levels of the PFS contents deferred to CMC review.

A. Syringe

NOTE: Sterility and endotoxin levels of the final combination product (filled syringes) deferred to CMC review. Per Module 3.2.P.7 [MnB Bivalent (b) (4)], “Sterilization of the syringes is performed with (b) (4) according to (b) (4). The syringes are received ready-to-use, (b) (4).”

Reviewer Comment: Table 3.2.P.7-5 states (b) (4) residuals are evaluated on a minimum of (b) (4) of syringe barrels (b) (4) (see [Section XI](#) of this memo). However, no information is provided regarding methods or acceptance criteria. Pfizer should clarify. See **IR#1.6b**. (b) (4) residuals are also evaluated by the supplier, based on the Certificates of Analysis for (b) (4) and (b) (4) syringe barrels provided in Module 3.2.R.

Information Request #1.6b	Date Sent: June 30, 2023	Date/Sequence Received: July 14, 2023 / 0033
IR Comment	<p>Module 3.2.P.7 [MnB Bivalent (b) (4)] Table 7 lists quality control testing performed on the syringe barrels. Please address the following:</p> <ul style="list-style-type: none"> a. ... b. You indicate that (b) (4) residuals are evaluated on a minimum of (b) (4) of incoming syringe barrels (b) (4). Please confirm that this test includes evaluation of both (b) (4) (b) (4) and (b) (4) and clarify the test method and acceptance criteria. This information is being requested since these residuals may be harmful beyond certain limits (refer to (b) (4)). 	
Sponsor Response	<p>b. Two test methods are used for evaluation of (b) (4) residuals.</p> <div style="background-color: #cccccc; height: 600px; width: 100%; display: flex; align-items: center; justify-content: center; font-size: 100px; font-weight: bold;"> (b) (4) </div>	

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

B. Vial Adapter

510(k) Number(s):	(b) (4)
Is contact classification of proposed device ^(b)	(b) (4)
evaluate the following:	yes
If device is sterilized with (b) (4) are of (b) (4) acceptable?	n/a
Ensure endotoxin limits are consistent with proposed administration route	n/a

XI. EPR Control Strategy

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

(b) (4)

Reviewer Comment: See review of response to **IR#1.4** below regarding incoming acceptance activities for the plunger rod and finger grip.

Information Request #1.4	Date Sent: June 30, 2023	Date/Sequence Received: July 14, 2023 / 0033
IR Comment	You provided only limited information regarding the plunger rod and finger grip (composition and biocompatibility per (b) (4)) in Modules 3.2.P.2.4 and 3.2.P.7 [MnB Bivalent (b) (4)]. Although these components are not product contacting, adequate information is still needed in your submission for these components. Please provide further device description for these components (e.g., dimensions, engineering drawings, etc.) as well as description of the component requirements and control strategy, with accompanying relevant documentation (e.g., COA or COC from supplier).	
Sponsor Response	<p>The polypropylene plunger rod is a component of the delivery device that is classified per (b) (4) (b) (4) as a surface device with intact skin contact. The plunger rod is manufactured by (b) (4) (b) (4) has shown the plunger rod fulfills the biological requirements of (b) (4) for cytotoxicity, sensitization, irritation and (b) (4) For informational purposes, the plunger rod is illustrated in Figure 1. Updated drawings will be maintained onsite at the manufacturing location. During incoming inspection of the polypropylene plunger rods, an identification test and a check of the manufacturer's certification are performed. The supplier states conformance to the specifications and/or drawings for the visual, dimensional and functional characteristics on the manufacturer's certification. A certificate of conformance of the (b) (4) plunger rod is provided in CoC – Plunger Rod – (b) (4)</p> <p>The polypropylene finger grip is a component of the delivery device that is classified per (b) (4) (b) (4) as a surface device with intact skin contact. The finger grip is manufactured and supplied by (b) (4) (b) (4) has shown the finger grip fulfills the biological requirements of (b) (4) for cytotoxicity (compliant to (b) (4) sensitization and irritation. For informational purposes, the finger grip is illustrated in Figure 2. Updated drawings will be maintained on-site at the manufacturing location. During incoming inspection of the polypropylene finger grips, an identification test and a check of the manufacturer's certification are performed. The supplier states conformance to the specifications and/or drawings for the visual, dimensional and functional characteristics on the manufacturer's certification. A certificate of analysis of the APE finger grip is provided in CoA – Finger Grip – (b) (4)</p>	

Reviewer Comments	Referenced figures added to Appendix 1 of this review memo.
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Information Request #1.6a	Date Sent: June 30, 2023	Date/Sequence Received: July 14, 2023 / 0033
IR Comment	<p>Module 3.2.P.7 [MnB Bivalent (b) (4)] Table 7 lists quality control testing performed on the syringe barrels. Please address the following:</p> <p>a. The testing includes a functionality test preformed on (b) (4) However, you did not describe what this test entails. Please provide additional information on what is involved in the functionality test, including a description of methods, specifications, and acceptance criteria. This information is being requested to understand how this quality control test contributes to your overall EPR control strategy.</p> <p>b. ...</p>	
Sponsor Response	<p>a. The functionality test performed on (b) (4) test. This test is performed to verify syringe functionality as part of incoming inspection quality controls. The (b) (4) test is used to ensure the syringe barrel is (b) (4) proof and prevents outside contamination, thus maintaining a sterile barrier.</p> <p>The steps to perform the (b) (4) test are as follows:</p> <div style="text-align: center; font-size: 48pt; font-weight: bold;">(b) (4)</div> <p>Table 1. Functionality Test for Incoming Syringe Barrels</p> <div style="text-align: center; font-size: 48pt; font-weight: bold;">(b) (4)</div>	
Reviewer Comments	Response is acceptable.	

XII. Packaging, Stability, Shipping

A. Packaging

Per Module 3.2.P.3.5 [MenABCWY], "The MenABCWY vaccine is provided in a kit comprising a single dose of the lyophilized MenACWY-TT drug product component in a 2 mL clear glass vial, the MnB bivalent (b) (4) MnB) drug product component in a 1 mL pre-filled syringe (PFS) and a 13 mm vial adaptor.

B. Shelf life

Proposed expiry/shelf-life:	24 months (MnB Bivalent (b) (4) Drug Product PFS)
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Storage conditions:	5 ± 3°C
Accelerated aging – duration and storage conditions:	(b) (4)
Real-time aging – duration and storage conditions:	24 months at 5±3°C in the tip-up orientation

Essential Performance Requirement (Stability Indicating)	Specification	Evaluated in Stability Program?
(b) (4)	Container closure integrity: pass	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
	(b) (4)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
	(b) (4)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

Pfizer submitted information regarding primary (formal stability studies to establish shelf life and demonstrate stability; (b) (4) lots of MnB Bivalent (b) (4) Drug Product PFS) and supporting (additional relevant stability studies from product development (b) (4) lots of MnB Bivalent (b) (4) Drug Product PFS and (b) (4) Trumenba lots) stability studies.

Table 3.2.P.8.3-1. Summary of Long Term (5 ± 3 °C) Drug Product Component Stability Studies

Lot Number	Manufacture Site	Lot Size	Syringe	Lot Designation	Data Available	Data Table Location
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

Table 3.2.P.8.3-2. Summary of Long Term (5 ± 3 °C) Trumenba Lot Stability Studies

Lot Number	Manufacture Site	Lot Size	Lot Designation	Data Available	Data Table Location
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

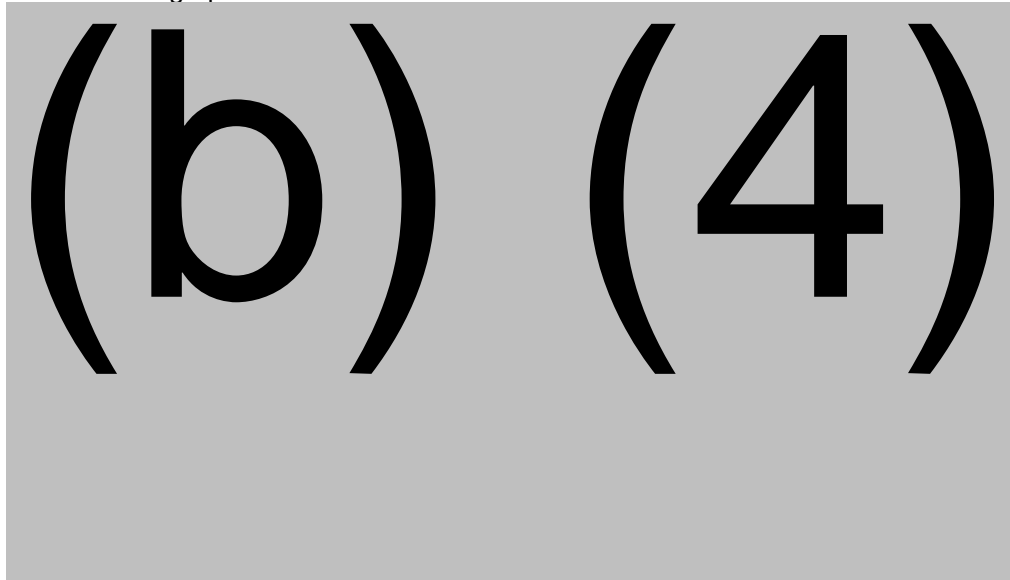
Dose Accuracy

Pfizer uses container closure integrity testing as an indicator of extractable volume in the stability program. CCIT was evaluated in the stability program as tabulated below (highlight indicates available data).

Study	Lots	Time Points (months)	Results
(b) (4)	(b) (4)	(b) (4)	(b) (4)

Study	Lots	Time Points (months)	Results
(b) (4)			

(b) (4)
Per Module 3.2.P.7 [MnB Bivalent (b) (4)] and [MenABCWY], (b) (4) were evaluated for samples from clinical (b) (4) and process validation/primary stability (b) (4) (b) (4) lots stored 5±3 °C over 24 months using a 25G 5/8 needle. All samples met acceptance criteria. See [Appendix 2](#) of this memo for graphs of the data.



Reviewer Comment: Pfizer provided data to demonstrate the maintenance of (b) (4) over the proposed shelf life (24 months) for the (b) (4)-MnB PFS itself, but the data for (b) (4) post-reconstitution only extends to 18 months. Pfizer should provide information on whether 24-month data will become available. See **IR#1.5** below.

Information Request #1.5	Date Sent: June 30, 2023	Date/Sequence Received: July 14, 2023 / 0033
IR Comment	<p>Please address the following regarding the stability data provided in Module 3.2.P.7 [MnB Bivalent (b) (4)] and [MenABCWY]:</p> <p>a. You provided data to demonstrate maintenance of (b) (4) for the MnB Bivalent (b) (4) PFS (before and after reconstitution to make MenABCWY) after storage. You provided data for the MnB Bivalent (b) (4) PFS over the entire proposed shelf life of 24 months. However, the (b) (4) data for MenABCWY only extends to 18 months. Please clarify when (b) (4) data for MenABCWY at 24 months will become available. This information is needed to ensure that syringeability is maintained for the final MenABCWY combination product at expiry.</p> <p>b. According to Module 3.2.P.8.2 [MnB Bivalent (b) (4)] and [MenABCWY], your stability programs do not include evaluation of (b) (4) which you list as in Modules 3.2.P.2.4 EPRs for the MnB Bivalent (b) (4) PFS and the MenABCWY final combination product. EPRs may be stability indicating because these factors can be impacted by external stressors, including aging and environmental conditions. Therefore, it is important to ensure EPRs are maintained at expiry. Please establish specifications and acceptance criteria for (b) (4) (b) (4) (b) (4) in your stability program.</p>	

**Sponsor
Response**

a. Results for MenABCWY (b) (4) (b) (4) (b) (4) tests up to 24 months at $5 \pm 3^{\circ}\text{C}$ are presented in Figure 1 and Figure 2. All measured MenABCWY (b) (4) results are within the design input requirement of not more than (b) (4) with the highest recorded value of (b) (4). These data sets support Pfizer's conclusion that syringeability for MenABCWY vaccine will maintain acceptable performance over the proposed shelf life and storage conditions. Section 3.2.P.2.4 Container Closure System [MenABCWY] has been updated to include the (b) (4) data at 24 months as well in updated Figures 3.2.P.2.4-3 and 3.2.P.2.4-4.

(b) (4)

	<p>b. (b) (4) is a functional attribute defined as the (b) (4) (b) (4) was identified as an EPR for both the MnB Bivalent (b) (4) drug product component and MenABCWY vaccine with an acceptance criterion of NMT 20 N in Section 3.2.P.2.4 Container Closure System [MnB Bivalent (b) (4)] and Section 3.2.P.2.4 Container Closure System [MenABCWY]. This criterion was extensively challenged throughout several stages of MenABCWY development as well as over the proposed shelf-life by design verification studies. These studies included the use of a 25G needle, both types of syringes (b) (4) and the use of a vial adapter. Acceptance criterion of (b) (4) was used across all design verification studies that included (b) (4) testing. (b) (4) states that the parameters (aging and environmental conditions) should be assessed to determine whether (b) (4) is stability indicating.</p> <p>Based on the data presented in 3.2.P.2.4 Container Closure System [MnB Bivalent (b) (4)] and Response to Query 5a above, aging assessments of (b) (4) were conducted across 24 months shelf-life for (b) (4) batches of MnB Bivalent (b) (4) drug product component and (b) (4) batches of MenABCWY. (b) (4) results of all batches tested were well below the (b) (4) limit with no apparent increase over time that would indicate that (b) (4) would approach or exceed the acceptance criteria at expiry.</p> <p>In addition, both the MnB Bivalent (b) (4) drug product component and MenABCWY vaccine were exposed to worst-case environmental conditions during a shipping validation study that confirmed acceptable (b) (4) results (b) (4) that were comparable to those obtained in aging studies. The results of shipping validation were previously provided in Section 3.2.P.3.5.8.1 of 3.2.P.3.5 Process Validation and/or Evaluation, Shipping Validation [MenABCWY].</p> <p>Given the totality of the (b) (4) data for both the MnB Bivalent (b) (4) drug product component and MenABCWY vaccine, inclusive of aging and exposure to worst-case environmental conditions, review of the data does not suggest that the (b) (4) attribute is stability-indicating. Sufficient data has been collected to demonstrate this attribute is well controlled and does not need to be tested routinely or as part of a formal stability program for this designated EPR. Moreover, the control strategy includes controls on the incoming components which ensure (b) (4) will remain consistent for commercial product.</p> <p>SUPPORTING DOCUMENTATION New or Replaced Supporting Documentation Section 3.2.P.2.4 Container Closure System [MnB Bivalent (b) (4)], Replaced, sequence 0001 (updated due to the Response to Query 1) Section 3.2.P.2.4 Container Closure System [MenABCWY], Replaced, sequence 0001 Previously Submitted Supporting Documentation Section 3.2.P.7 Container Closure System [MnB Bivalent (b) (4)], sequence 0001 Section 3.2.P.3.5 Process Validation and/or Evaluation, Shipping Validation [MenABCWY], sequence 0001</p>
Reviewer Comments	<i>Response is acceptable.</i>

C. Shipping

Essential Performance Requirement (Stability Indicating)	Specification	Evaluated after Shipping/ Transportation?
(b) (4)		

(b) (4)

In Module 3.2.P.3.5 [MenABCWY], Pfizer provided a high-level tabulation of the shipping process with the associated modes qualified for the global supply chain map of the MenABCWY vaccine (below).

(b) (4)

Pfizer conducted a simulated shipping study to “to verify that there were no adverse effects on the quality of the MenACWY-TT drug product component, (b) (4)-MnB, and the MenABCWY vaccine drug product as a result of the mechanical and environmental stresses associated with the transportation/shipping processes.” The study simulated “the validated shipping process for shipping and distribution of the MenACWY-TT drug product component, unassembled, and unlabeled vials packaged in trays, and (b) (4)-MnB drug product component, unassembled, and unlabeled syringes packaged in tubs.”

The simulated packaging configuration consisted of (b) (4)-MnB PFS (b) (4) (b) (4) which is worst case because it provides minimal protection from physical damage. Pfizer states that “the drug product in the study was contained in its worst-case configuration with regards to its physical protection from damage and is considered supportive of the shipping process for the MenABCWY vaccine combination product in the final packaging.”

(b) (4)

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

**Table 3.2.P.3.5-20. MenABCWY Vaccine Drug Product Simulated Transportation
Study Product Quality Test Results**

Analytical Test	Acceptance Criteria	Test	Control
(b) (4)			

XIII. Quality Systems Assessment

Quality System Approach:

- ☒ [Streamlined – Drug GMP Based](#)
☐ [Streamlined – Device QSR Based](#)
☐ Other (Describe)

Streamlined – Drug GMP Based

Device GMP Requirement	Responsible Firm(s):	Acceptable?	Reviewer Comments
21 CFR 820.20 Summary of Management Responsibility		Deferred to OCBQ/DMPQ Reviewer	
21 CFR 820.30 Summary of Design Controls		<input type="checkbox"/> Yes <input type="checkbox"/> No	A narrative of how the requirements of 21 CFR 4.4(b) have been met is provided in Module 3.2.R.2. Descriptions are acceptable.
21 CFR 820.50 Summary of Purchasing Controls		<input type="checkbox"/> Yes <input type="checkbox"/> No	
21 CFR 820.100 Summary of Corrective and Preventive Actions		Deferred to OCBQ/DMPQ Reviewer	
21 CFR 820.170 Summary of Installation	N/A		
21 CFR 820.200 Summary Servicing	N/A		

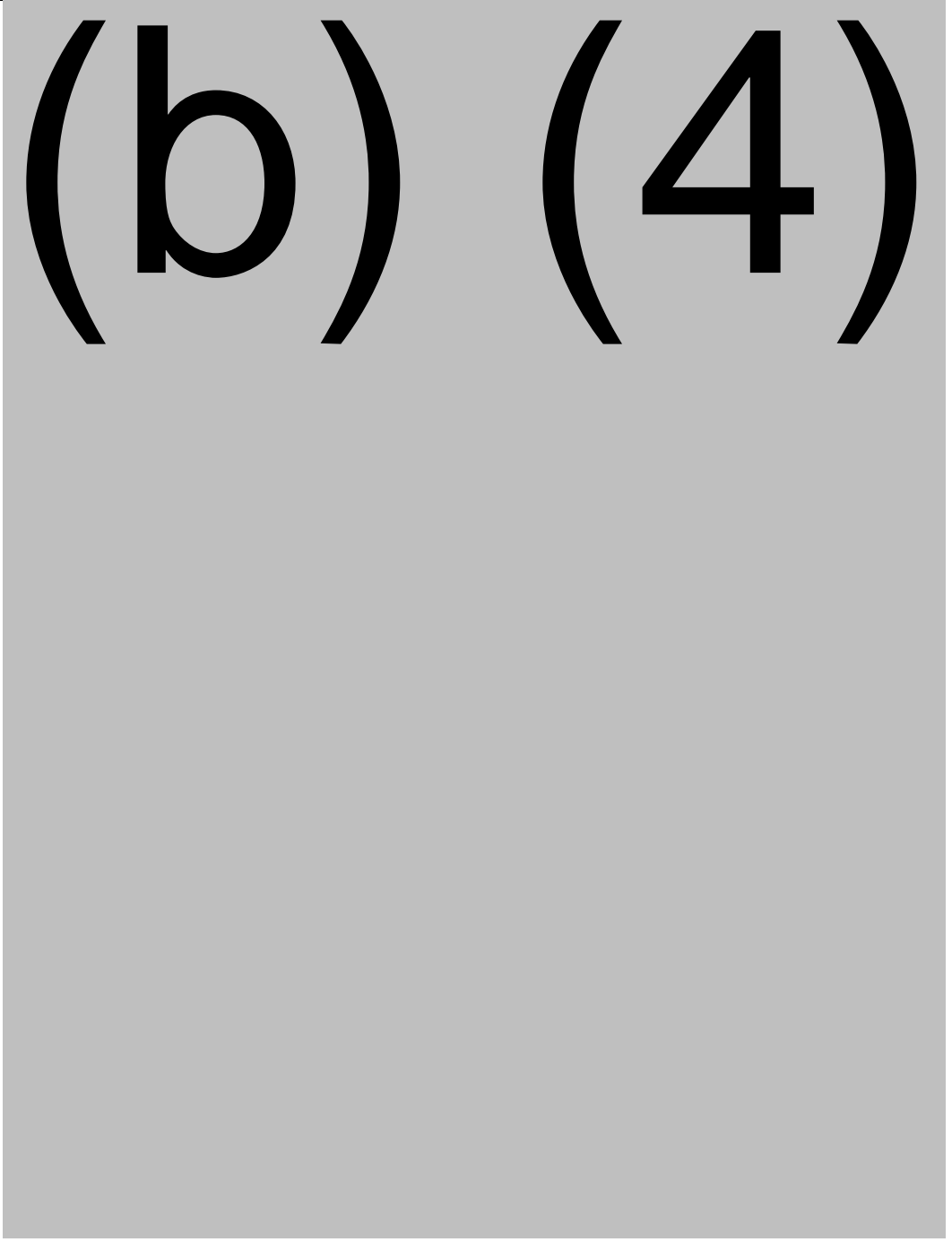
XIV. Labeling

Labeling review is deferred to the other disciplines and management.

XV. Appendices

A. Appendix 1 – Engineering Drawings

(b) (4)



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

(b) (4)

3.2.P.2.4 Container Closure [MenABCWY]

Table 3.2.P.2.4-3. Summary of (b) (4).MnB and MenACWY-TT DP Component
Lots and Usage

(b) (4)

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