

BLA STN 125770

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

**Lisa Parsons/Ph.D./Laboratory of Bacterial Polysaccharides/Division of Bacterial
Parasitic and Allergenic Products/Office of Vaccines Research and Review**

**James E. Keller/Ph.D./Laboratory of Respiratory and Special Pathogens/Division
of Bacterial Parasitic and Allergenic Products/Office of Vaccines Research and
Review**

**Lunhua Liu/Ph.D./Laboratory of Bacterial Polysaccharides/Division of Bacterial
Parasitic and Allergenic Products/Office of Vaccines Research and Review**

**Kathryn Matthias/Ph.D./Laboratory of Bacterial Polysaccharides/Division of
Bacterial Parasitic and Allergenic Products/Office of Vaccines Research and
Review**

1. **BLA#:** STN 125770
2. **APPLICANT NAME AND LICENSE NUMBER:** Pfizer Ireland Pharmaceuticals
3. **PRODUCT NAME/PRODUCT TYPE**
PENBRAYA
Meningococcal Groups A, B, C, W, and Y Vaccine
4. **GENERAL DESCRIPTION OF THE FINAL PRODUCT**
 - a. Vaccine
 - b. 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.
 - c. Each 0.5 mL dose contains 60 µg each of MnB (b) (4) subfamily A and B proteins, and 5 µg each of Meningococcal polysaccharide serotypes A, C, W, and Y conjugated to about 44 µg of tetanus toxoid in total. Potency of the proteins is measured by serum bactericidal assay. The (b) (4) of the polysaccharide serotypes in the drug product is measured by (b) (4)
 - d. Intramuscular injection
 - e. Prevention of invasive disease caused by *Neisseria meningitidis* groups A, B, C, W, and Y in individuals 10 through 25 years of age.
5. **MAJOR MILESTONES**
 - Acknowledgement Letter – 07 November 2022
 - First Committee Meeting – 09 November 2022
 - Filing Meeting – 05 December 2022
 - Mid-Cycle Meeting – 05 April 2023
 - Late-Cycle Meeting – 28 June 2023
 - Request for reference product designation received 21 October 2022; CBER's reference product determination board met on 28 September 2023 and concurred with the CMC reviewer's recommendation to grant the designation. Upon approval, the product will be designated as a reference product and the associated exclusivity periods will be based on the date of first approval.
 - PDUFA Action Due Date – 20 October 2023

6. **CMC/QUALITY REVIEW TEAM**

Reviewer/Affiliation	Section/Subject Matter
James Keller, OVRR/DBPAP/LRSP	3.2.S.1 – 3.2.S.7.3 (b) (4) (b) (4) Manufacture 3.2.R Batch Record review of (b) (4) (b) (4)
Lisa Parsons, OVRR/DBPAP/LBP	1.3.5.3 Exclusivity Request 3.2.S.1 – 3.2.S.7 MnB Subfamily A & B, MenAAH-TT, MenCAH-TT, MenW-TT, and MenY-TT (b) (4) 3.2.P.1 – 3.2.P.7 MnB Bivalent (b) (4) MenACWY-TT lyophilized and MenABCWY liquid Drug Products 3.2.R Associated Batch Records and Comparability Protocols
Lunhua Liu, OVRR/DBPAP/LBP	3.2.P.5.2 Analytical Procedures MnB (b) (4) Drug Product – (b) (4) (b) (4) Potency, and (b) (4) 3.2.P.5.3 Validation of Analytical Procedures MnB (b) (4) Drug Product -- (b) (4) and (b) (4) Potency
Kathryn Matthias, OVRR/DBPAP/LBP	4.2.1.1 Primary Pharmacodynamics 4.2.3.2 – 4.2.3.5, as pertains to immunogenicity analyses 5.3.1.4 Reports of Biopharmaceutic Studies 5.3.5 Reports of Efficacy and Safety Studies (as related to serology endpoints)

7. **INTER-CENTER CONSULTS REQUESTED**

No inter-center consults were requested.

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
21-Oct-2022	STN 125770/0	Reviewed by LP, JK, LL, KM
17-Nov-2022	STN 125770/0.1	CMC Stability Data (LP)
13-Jan-2023	STN 125770/0.3	Response to Tetanus Toxoid (TT) IRs sent 16-Dec-2022 (JK)
23-Jan-2023	STN 125770/0.4	Response to serology IRs sent 20-Dec-2022 (KM)
9-Feb-2023	STN 125770/0.7	Response to serology IR sent 10-Jan-2023 (KM)
3-Apr-2023	STN 125770/0/11	Response to serology IR sent 03-Mar-2023 (KM)
14-Apr-2023	STN 125770/0.12	Response to CMC IRs sent 16-Mar-2023: QQ1–5 (LP) QQ6–7 (JK) QQ8 (LL)
28-Apr-2023	STN 125770/0.13	Response to serology IR sent 10-Apr-2023 (KM)
1-May-2023	STN 125770/0.14	Response to CMC IR related to (b) (4) Test, sent 6-Apr-2023 (LP)
5-May-2023	STN 125770/0.15	Response to CMC IRs sent 24-Apr-2023 (LP)
24-May-2023	STN 125770/0.16	Response to serology IRs sent 10-Jan-2023 and 03-Mar-2023 (KM)
30-May-2023	STN 125770/0.19	Response to TT IRs sent 16-May-2023 (JK)
12-June-2023	STN 125770/0.20	Response to exclusivity IR sent 31-May-2023 (LP)
21-June-2023	STN 125770/0.22	Response to CMC IRs sent 6-Jun-2023 (LP, JK)
26-June-2023	STN 125770/0.23	Response to statistical IRs sent 12-Jun-2023 (LP, LL)
14-July-2023	STN 125770/0.24	Response to TT IRs sent 29-Jun-2023 (JK)
31-July-2023	STN 125770/0.25	Additional response to IRs sent 12-Jun-2023: QQ1 (LP)
28-July-2023	STN 125770/0.26	Response to IRs sent 13-Jul-2023 (LP)
9-Aug-2023	STN 125770/0.28	Response to IR sent 26-Jul-2023 (LP)
11-Aug-2023	STN125770/0.29	Response to IR sent 6-Jun-2023 (JK)
15-Aug-2023	STN 125770/0.31	Additional response to IR sent 24-Apr-2023 (LP)

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

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
DMF (b) (4)	(b) (4) — (b) (4)	(b) (4) Glass Prefillable Syringe (PFS): Syringe, Plunger Rod, Plunger Stopper	Yes	Authorization for FDA to review information pertaining to (b) (4) Glass Prefillable Syringe
DMF (b) (4)	(b) (4) (b) (4)	Primary Packaging Material Syringes as Manufactured in (b) (4)	Yes	Authorization for FDA to review information pertaining to (b) (4) 1 mL glass syringe with (b) (4) rigid cap Luer Lock connection
DMF (b) (4)	(b) (4)	Syringe tip cap elastomer, plunger stopper	Yes	Authorization for FDA to review information pertaining to Syringe tip cap composed of gray (b) (4) (b) (4) (b) (4) elastomer and 1–3 mL plunger stopper composed of gray (b) (4) (b) (4) elastomer
DMF (b) (4) (b) (4)	(b) (4)	Primary Packaging Material	Yes	Authorization for FDA to review information pertaining to 2 mL Type (b) (4) borosilicate glass vial, 13 mm finish
DMF (b) (4)	(b) (4)	(b) (4)	Yes	Authorization for FDA to review information pertaining to 2 mL Type (b) (4) borosilicate glass vial, 13 mm finish
DMF (b) (4)	(b) (4)	Rubber Compounds		Authorization for FDA to review information pertaining to Compound (b) (4)

IND 13812	Pfizer, Inc.	TRUMENBA	No	Pharmacology and Toxicology data (in association with pre-clinical immunogenicity studies) and qualification/validation data for serum bactericidal assays (KM)
(b) (4)	Pfizer, Inc.	NIMENRIX	No	Pharmacology and Toxicology data (in association with pre-clinical immunogenicity studies; KM)
IND 17319	Pfizer, Inc.	PENBRAYA	No	Qualification/validation data for serum bactericidal assays (KM)
BLA 125549	Pfizer, Inc.	TRUMENBA	No	Qualification/validation data for serum bactericidal assays (KM)

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

Pfizer Ireland Pharmaceuticals (Pfizer) is seeking licensure of PENBRAYA, a penta-valent meningococcal conjugate vaccine indicated for 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. PENBRAYA consists of a lyophilized vaccine component (Meningococcal (Groups A, C, Y, W) Conjugate Vaccine (MenACWY)) and a liquid vaccine component (Meningococcal Group B Vaccine (MenB)). The MenACWY component is reconstituted with the MenB vaccine component immediately before administration. Active ingredients consist of four meningococcal capsular polysaccharides (PS) individually conjugated to the carrier protein Tetanus Toxoid (TT) and two lipidated factor H binding protein (fHbp) variants from *Neisseria meningitidis*. Pfizer grows *N. meningitidis* and purifies the polysaccharides from the capsules of serogroups A, C, W and Y. The TT carrier protein is an inactivated form of tetanus toxin expressed by *Clostridium tetani*. Pfizer reduces the PSs in size via microfluidization, then reacts a subset of (b) (4) They further process A and C by (b) (4) with an adipic acid dihydrazide linker. (b) (4) (b) (4) TT in the presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDAC). Pfizer conjugates the (b) (4) in W and Y (b) (4) TT. The manufacturing process and manufacturing facilities used for the MenB (b) (4) Drug Product (DP) are the same as for the U.S.-licensed vaccine TRUMENBA™ (STN 125549). The fHbp variants from *N. meningitidis* serogroup B are recombinantly expressed individually in *Escherichia coli*. One fHbp protein is from subfamily A and one from subfamily B (A05 and B01, respectively). Production strains are grown in defined fermentation growth media to a specific density. The recombinant proteins are extracted

from the production strains and purified through a series of column chromatography steps. Polysorbate 80 (PS80) is added (b) (4) and is present in the final DP.

The polysaccharides and TT are produced at the (b) (4) manufacturing site. The monovalent (b) (4) conjugates are produced at the (b) (4) site in (b) (4) (b) (4). The MenACWY DP is formulated and filled at the (b) (4) site in (b) (4) (b) (4). The MenB DP is formulated and filled at the (b) (4) site.

Pfizer used the principles of quality-by-design detailed in ICH Q8 (R2) and the Failure Mode Effects Analysis (FMEA) in ICH Q9 to evaluate the process parameters and establish the in-process attributes and parameter ranges for establishment of specifications. Critical Process Parameters (CPP) and Critical Quality Attributes (CQA) were established throughout the manufacturing process for intermediates, DS and DP. In-Process Controls (IPC) were established where appropriate. Key Process Attributes (KPA) and Key Operating Parameters (KOPs) were also established.

Release tests and in-process tests were developed and validated as appropriate for all intermediates, DSs, and DP. The testing panels adequately measure quality and safety and provide a baseline of physiochemical and biological attributes. Some release tests have been incorporated into the stability testing program for intermediates, DSs, and DP. Hold times have been established and are supported by validation data.

The polysaccharides are stored at (b) (4) in (b) (4) (b) (4). Stability data support a shelf life of up to (b) (4) months for all MenACWY serogroups. Stability data submitted for the TT intermediate, stored at (b) (4) in (b) (4) (b) (4), support a shelf life of (b) (4) months. The monovalent (b) (4) conjugates are stored in (b) (4) at (b) (4) (b) (4) with a shelf life of (b) (4). The MenB fHbp proteins are stored in (b) (4) (b) (4) at (b) (4) with a shelf life of (b) (4). The information submitted supports the proposed shelf lives. The DP is stored as a single-dose vial of lyophilized MenACWY-TT vaccine component with the accompanying prefilled syringe of MenB fHbp suspension vaccine component. The proposed shelf lives of 18 months for the MenACWY-TT component and 24 months for the MenB component when stored at 2–8°C is supported by the information submitted to the file.

Antibody-dependent complement-mediated killing of encapsulated *N. meningitidis* constitutes the primary mechanism involved in host protection from invasive meningococcal disease. Therefore, the human complement serum bactericidal assay (hSBA) is used to assess vaccine-induced antibody response and clinical efficacy. The primary endpoint for evaluating the efficacy of PENBRAYA is based on the demonstration of non-inferiority of PENBRAYA (via hSBA) to the licensed meningococcal MenACWY and MenB vaccines, MenACWY-CRM (e.g., Menveo™) and TRUMENBA, respectively. The hSBAs used to evaluate Phase 3 study samples were validated at the sites of clinical sample testing for anti-MenACWY and anti-MenB serological responses, (b) (4) and

the (b) (4) respectively. Two Phase 3 studies were conducted, including the pivotal Phase 3 study C3511001, in which immunogenicity of PENBRAYA was compared to that of Menveo and TRUMENBA in volunteers 10–25 years of age. The PENBRAYA vaccine met the primary and secondary efficacy objectives in study C3511001 and in all other clinical studies. The review prompted several information requests related to the standard operation procedure, validation, and assay quality control performance. Pfizer addressed these comments in amendments. Overall, the hSBA used in the evaluation of clinical endpoints for the Phase 3 studies were adequate for their intended uses.

We recommend approval of STN 125770/0.

B. RECOMMENDATION

I. APPROVAL

Based on the CMC information and data provided in this application, we recommend approval of this BLA. Lot release will be performed via protocol review only. Please refer to the DBSQC reviewer's memo for additional information on the Lot Release Protocol.

DP (b) (4) Manufacturing Facilities

Manufacturer	Roles
(b) (4)	

(b) (4)

Comparability Protocols which will be included upon approval of this BLA are for:

- Preparation, qualification, storage and shipping of (b) (4)
- Lifetime extension for (b) (4)
- Lifetime extension for (b) (4)
- Lifetime extensions for (b) (4)

(b) (4)

Updates will be reported in the (b) (4) Report or, if the acceptance criteria are not met, Pfizer will either not implement the change or will supply a PAS to justify the change.

II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Lisa Parsons, PhD Biologist CBER/OVRR/DBPAP/LBP	Concur	
James Keller, PhD Biologist CBER/OVRR/DBPAP/LRSP	Concur	
Lunhua Liu, PhD Biologist, CBER/OVRR/DBPAP/LBP	Concur	
Kathryn Mattias, PhD Biologist CBER/OVRR/DBPAP/LBP	Concur	
Willie F. Vann, PhD Chief CBER/OVRR/DBPAP/LBP	Concur	
Jay E. Slater, MD Director CBER/OVRR/DBPAP	Concur	

Review of CTD

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Module 3

Reviewed by JK

3.2.S DRUG SUBSTANCE (b) (4)

3.2.S.1.1 – 1.3 Nomenclature, Structure and General Properties

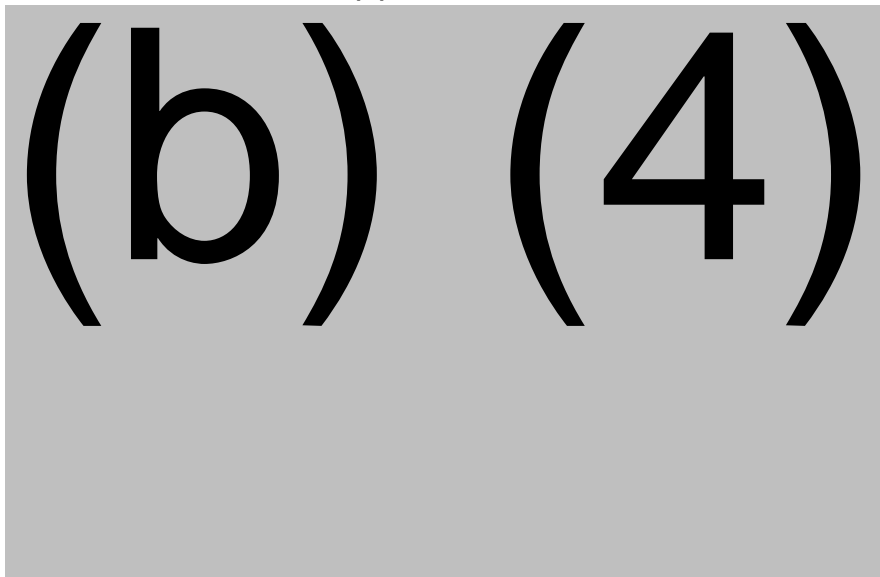
(b) (4)



3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

(b) (4)



(b) (4)



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

(b) (4)

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

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

MnB Bivalent (b) (4) is a sterile liquid suspension of the (b) (4) subfamily A and B protein (b) (4) containing (b) (4) of each protein in (b) (4) (b) (4)

(b) (4) the sponsor refers to the drug product (DP) as (b) (4) MnB (b) (4) MnB).

(b) (4) MnB is used to reconstitute the lyophilized MenACWY-TT DP component through a vial adapter. The sponsor fills (b) (4) MnB into 1-mL syringes, with a target fill volume of (b) (4) to ensure a nominal extractable volume of (b) (4) and a volume of injection of (b) (4) 0.5 mL. There is no manufacturing overage.

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

(b) (4)

3.2.P.2.1.2 Excipients

- (b) (4) pH 6.0 to provide pH control
- (b) (4) NaCl, to provide (b) (4) suitable for injection
- (b) (4) PS80, to prevent adsorption of protein to contact surfaces
- AlPO₄ (b) (4) stabilizer that binds to the proteins

3.2.P.2.2 Drug Product

- MenB (b) (4) subfamily A, (b) (4)
- MenB (b) (4) subfamily B, (b) (4)
- (b) (4) pH 6.0
- (b) (4) NaCl

- (b) (4) PS80
- AlPO_4 (b) (4)

3.2.P.2.2.1 Formulation Development

Pfizer uses the TRUMENBA commercial manufacturing process to produce (b) (4)-MnB. (b) (4)-MnB differs from TRUMENBA in the (b) (4) and plunger stopper placement of the DP syringes.

3.2.P.2.2.2 Overages

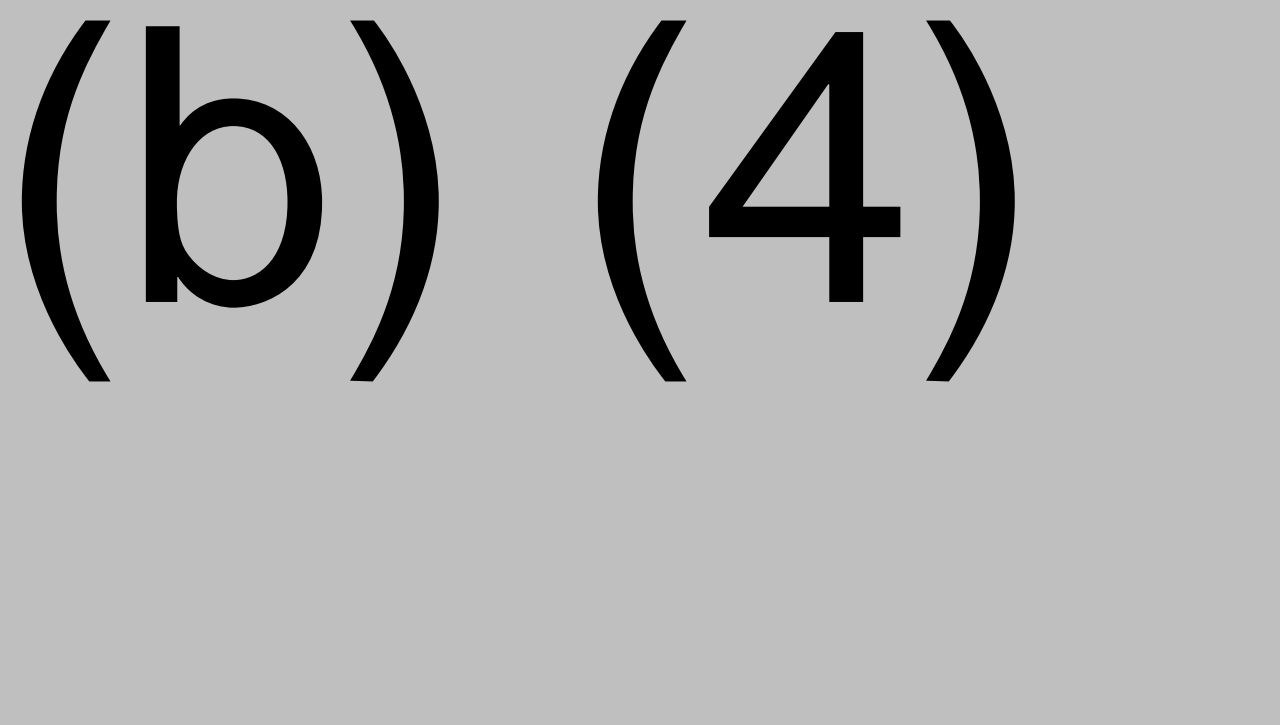
Pfizer states there are no overages for (b) (4)-MnB.

3.2.P.2.2.3 Physicochemical and Biological Properties

When formulated into the DP with a pH of (b) (4) and subjected to various stresses, the MnB proteins became (b) (4) after (b) (4) and exhibit a decrease (b) (4). (b) (4) Pfizer found that addition of AlPO_4 , even at (b) (4) maintained (b) (4). Pfizer further tested conditions to determine the amount of AlPO_4 , NaCl, PS80, protein, and pH to use. They also (b) (4) samples with (b) (4) and (b) (4) (potential syringe leachables) and showed the DP was unaffected at (b) (4) times the amount present in syringes.

To determine the syringe volume of the (b) (4)-MnB DP, Pfizer measured the (b) (4) volume in the (b) (4)-MnB DP syringes with the syringe adapter attached (b) (4) the extractable volume for the MenACWY-TT vial (b) (4) and concluded a prefilled syringe volume of (b) (4) was optimal.

3.2.P.2.3 Manufacturing Process Development



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

(b) (4)

3.2.P.2.4 Container Closure System

See 3.2.P.7 for a description of the Container Closure System. Pfizer uses syringes from (b) (4) different manufacturers and stoppers from (b) (4) (b) (4) from (b) (4) different locations. They showed the components were interchangeable based on materials of construction, dimension, how well they worked on the filling lines, biocompatibility, and stability of the DP in the different syringes.

Pfizer included a description of their extractables studies on the plunger stopper and tip cap and listed the potential extractables in the syringe barrel, syringe needle (b) (4) and needle provided by the vendors. The extractables studies involved (b) (4) (b) (4)

Tables 3.2.P.2.4-5 to -8 list the extractables. Most extractables from the plunger stopper were calculated to be present at (b) (4) the exceptions being (b) (4)

No compounds were identified from the tip cap in (b) (4) leachables study is underway on (b) (4) DP lots. During the first (b) (4) Pfizer identified (b) (4) as expected since these are used in manufacture of the syringes, but no unexpected leachables.

Reviewer Comment (LP): *In submission 0.15, in addition to a response to the 05May23-IR sent 24 April 2023 (see below), Pfizer removed the information regarding the syringe needle and syringe needle (b) (4) since they are not included in the MenABCWY kit. Pfizer stated the information was “inadvertently copied from another dossier.”*

Pfizer also analyzed (b) (4) extractable volume, plunger stopper placement and movement, and functional attributes post-translation as described in different sections of the submission and summarized in Table 3.2.P.2.4-14. Pfizer also included figures (3.2.P.2.4-3 and -5) showing the (b) (4) in different lots up to (b) (4) While (b) (4) generally increased over time, it stayed well below the (b) (4) cutoff.

Information Request

05May23-IR

[Sent by CBER 24 April 2023. Response received 05 May 2023 (STN 125770/0.15)]

CBER Question 1

In Section 3.2.P.2.4.2.1.3, you provided summaries of your Extractables and Leachables studies. However, you have not provided the Extractable and Leachable reports. Please provide the full reports, not just descriptions, for all the DP container closure components in contact with the Drug Product (DP),

including the report for the vial adapter, if applicable. Please include in each report the raw data on compounds identified and the level of each that was found.

Pfizer's Response to Question 1

Pfizer submitted 'Comprehensive Extractable and Leachable Summary Reports' for (b) (4) MnB DP (b) (4) and for MenACWY-TT DP (b) (4)

They also updated section 3.2.P.2.4 *Container Closure System* for (b) (4) MnB DP and MenACWY-TT DP to include the (b) (4) and (b) (4) timepoints, respectively. They did not perform E&L studies on the vial adapters due to the transient nature of contact during use, although they did test compatibility with the DP. In addition, Pfizer removed the needle and needle (b) (4) information under 3.2.P.2.4 for MnB DP since the final DP kit does not include a needle.

Reviewer Comment (LP): Pfizer submitted the requested material. I reviewed the extractables and leachables study reports under section 3.2.P.2.4 for each of the component DPs. The information provided is acceptable.

3.2.P.2.5 Microbiological Attributes

Pfizer fills filtered (b) (4)-MnB into sterile syringes to produce a sterile liquid suspension. They test for bioburden, endotoxin, and (b) (4) to ensure the DP remains sterile and the container closure is not compromised.

3.2.P.2.6 Compatibility

Pfizer has determined the MnB DP component is compatible with the syringe from stability studies with the syringes in tip-up orientation which demonstrate all acceptance criteria are met over time when stored at 2–8°C.

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

LP: Manufacture of (b) (4)-MnB is essentially the same as TRUMENBA with the exception of the (b) (4) and stopper placement. Pfizer demonstrated syringes filled with (b) (4) MnB with the (b) (4) and placement met all the parameters for manufacturability, performance, and safety of the DP. This is acceptable.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

(b) (4)

(b) (4)

3.2.P.3.2 Batch Formula

(b) (4)

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

LP: Pfizer's submitted batch formula matches the proposed final DP component formulation.

3.2.P.3.3 Description of Manufacturing Process

(b) (4)

(b) (4)

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

LP: Pfizer has established IPTs and tests sufficient to ensure product sterility and proper packaging.

3.2.P.3.4 Controls of Critical Steps and Intermediates

(b) (4)

(b) (4)

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

LP: The information provided in this section is largely the same as that under the TRUMENBA BLA, with the only differences being (b) (4) and stopper position. I find the information acceptable as submitted.

3.2.P.3.5 Process Validation and/or Evaluation

(b) (4)

(b) (4)

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

LP: Pfizer acceptably demonstrated control over all steps of (b) (4)-MnB manufacturing from filtering to filling, hold times, and shipping validations.

3.2.P.4 Control of Excipients

(b) (4)

(b) (4)

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

LP: The only (b) (4) excipient in the (b) (4)-MnB DP is AlPO₄. Pfizer's specifications are appropriate and adequately justified. I find the information in this section acceptable as submitted.

3.2.P.5 Control of Drug Product

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

(b) (4)

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

LP: Pfizer's acceptance criteria for the (b) (4)-MnB DP, and their justification, are appropriate. I identified no deficiencies and find the information in this section acceptable as submitted.

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

In a December 8, 2022 meeting with DBSQC, we agreed that DBSQC would review all the assays for ^{(b) (4)}-MnB DP other than (b) (4) Potency (b) (4) (b) (4) (b) (4) and Endotoxin assays, which DBPAP would review (LL) and are described below. Please refer to the DBSQC memo for descriptions and reviews of all other assays.

Reviewed by LL

Analytical Procedure – (b) (4) Potency

(b) (4)

(4)

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

(b) (4)

Overall Reviewer's Assessment of Sections 3.2.P.5.2 and 3.2.P.5

LL: The (b) (4) assays were characterized and validated. The specifications appear to be appropriate. The tests are likely adequate to detect meaningful changes of MnB DP and suitable as a release and stability testing. The (b) (4) (b) (4) is consistent with the (b) (4) method and suitable to determine the pyrogenicity of the MnB DP components.

Reviewed by LP

3.2.P.5.4 Batch Analyses

Pfizer submitted data on (b) (4) TRUMENBA DP lots made in 2016 to 2018 and (b) (4) (b) (4) -MnB DP component lots manufactured between 2019 and 2020 at (b) (4) (b) (4). The (b) (4) 2020 lots were all used for process validation and primary stability. All lots met acceptance criteria upon release.

3.2.P.5.5 Characterization of Impurities

Pfizer does not introduce additional impurities at the DP stage.

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

LP: I find the information in this section acceptable as submitted.

3.2.P.6 Reference Standards or Materials

Pfizer uses the same reference materials for the DP as for the MnB (b) (4) as described under Section 3.2.S.5.

3.2.P.7 Container Closure System

The container closure system (CCS) consists of a 1-mL Type (b) (4) borosilicate glass (b) (4) or (b) (4) syringe (b) (4) a tip cap by (b) (4) (b) (4) (b) (4) made of a latex-free (b) (4) elastomer, a plastic rigid tip cap assembly (b) (4) or (b) (4) Rigid Cap assembly (b) (4) and a 1–3 mL chlorobutyl rubber plunger stopper also (b) (4). The syringe, tip cap, and plunger are in contact with the product. Pfizer included tables of dimensions and representative drawings of the syringes, tip caps, tip cap assemblies, and plunger stoppers.

Pfizer receives the syringes sterile and ready-to-use. They perform visual, physical, functional, and (b) (4) tests on each syringe lot and perform glass, residual (b) (4) sterility, and endotoxin tests on (b) (4) lot of syringes each (b) (4). The final (b) (4) tests are also performed by the syringe manufacturers for each lot.

(b) (4) washes, (b) (4) and packages the plunger stoppers. (b) (4) then sterilizes them with (b) (4). Pfizer does visual inspection and identification of elastomer and (b) (4) by lot and accepts the manufacturer's sterility certificate for each lot. The plunger rod and finger grips are made of polypropylene and do not contact the product.

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

LP: I refer review of the schematics of the container closure system to DMPQ. The description here as it pertains to CMC reviewed by DBPAP is acceptable as submitted. For information regarding E&L studies please refer to module 3.2.P.2.4, above.

3.2.P.8 Stability

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

Pfizer submitted the following studies:

- Long term (LT) at (b) (4) in (b) (4) or (b) (4) syringes (under 125770/0.01) for:
 - (b) (4) on (b) (4) process validation lots and (b) (4) lot in different syringes for (b) (4)-MnB.
 - (b) (4) on (b) (4) TRUMENBA DP supportive stability lots
- Accelerated conditions of (b) (4) and (b) (4) (b) (4) for (b) (4) on all the (b) (4) lots listed above.
- (b) (4) (b) (4) on (b) (4) batch at (b) (4) and (b) (4) for (b) (4)
- (b) (4) (b) (4) (b) (4) to (b) (4) (b) (4) (b) (4)
- (b) (4) of data on (b) (4) lots exposed to (b) (4) cycles of (b) (4) and (b) (4) then (b) (4) then stored under LT conditions.
- (b) (4) of data on (b) (4) lot stored for (b) (4) at (b) (4) then stored under LT conditions.

There were no trends in appearance, container closure integrity, endotoxin, (b) (4) (b) (4) potency, pH, PS80 (b) (4) protein total, purity, or stability for the LT studies. Under accelerated conditions at (b) (4) purity drops to the minimum amount of (b) (4) at (b) (4) for all batches tested, but all other parameters show no trends.

Reviewer Comment (LP): (b) (4) potency under accelerated conditions was 'Pending' for (b) (4) and was not included for the remaining (b) (4) batches. It was also 'pending' at (b) (4) for (b) (4) and (b) (4) and 'Inadvertently missed' for the (b) (4) lots at the (b) (4) timepoint. I sent an IR requesting the pending information (see below). All criteria were met for all other conditions.

The proposed shelf life is (b) (4) at 2–8°C, but Pfizer demonstrated the DP was stable under all the conditions listed.

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

Post-approval, Pfizer will enroll a minimum of (b) (4) of the MnB Bivalent (b) (4) DP in the commercial stability program at 2–8°C for (b) (4) months with testing every 12 months. They will test for appearance, container closure integrity, (b) (4) (b) (4) potency, pH, PS80 (b) (4) (b) (4) total protein, and purity. Sterility will be tested at time zero and end of shelf life. These are the same as for TRUMENBA (STN 125549) except Pfizer dropped the (b) (4) test.

Reviewer comment (LP): (b) (4) will only change if the vaccine is not sterile, and the applicant will test sterility at end of shelf life. In addition, contamination will likely cause degradation and contamination of the DP which will affect other tests such as purity. I find not testing (b) (4) on stability to be acceptable.

Information Request

21June23-IR

[Sent by CBER 6 June 2023. Response received 21 June 2023 (STN 125770/0.22)].

CBER Question 2

In 3.2.P.8.3 Stability Data for MnB Bivalent (b) (4) DP, you have provided data to support the stability of your MnB DP under long-term, accelerated, and (b) (4) (b) (4) storage conditions. We note the following data appear to be incomplete or missing:

- 1. Under accelerated conditions:*
 - a. The results of the (b) (4) potency assay at 6 months for lots (b) (4) (b) (4) are all 'pending'.*
 - b. You have not provided in vivo potency data for lots (b) (4) (b) (4)*
- 2. Under long term conditions the (b) (4) potency is also 'pending' for lots (b) (4) and 24 months in both the initial submission and 125770/0.01.*

So that we can assess the stability of these lots and complete our review, please submit these data.

Pfizer's Response to Question 2

Pfizer submitted updated files summarizing the stability data (3.2.P.8.1) and adding the requested information (3.2.P.8.3) as well as updating incorrectly listed acceptance criteria for three lots to match the current specifications. The did not submit (b) (4) potency data for lots (b) (4) under accelerated conditions as it was only a characterization test at the time and only tested under long-term conditions.

Reviewer Comment (LP): (b) (4) potency under accelerated and long-term conditions did not demonstrate any trends and stayed within the acceptance criteria. This is acceptable.

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

LP: Pfizer has chosen assays that monitor both the physical and immunogenic properties of the DP. The submitted data indicate the DP is stable for 24 months at 2–8°C and up to (b) (4) at (b) (4) I find the information in this section acceptable as submitted.

Reviewed by LP

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 composed of *N. meningitidis* PS serotypes A, C, W, and Y, each conjugated to TT at ratios to PS of (b) (4) respectively. Pfizer formulates this DP component in (b) (4) trometamol (Tris) buffer with (b) (4) sucrose at (b) (4). Each lyophilized vial contains (b) (4) of each serotype and about (b) (4) of TT to ensure (b) (4) of each conjugate serotype and about (b) (4) of TT in a 0.5 mL dose when reconstituted. (b) (4)

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

(b) (4)

3.2.P.2.1.2 Excipients

- Trometamol (Tris base), (b) (4) to provide (b) (4) control
- Sucrose, (b) (4) as a cryoprotectant and stabilizer during lyophilization

3.2.P.2.2 Drug Product

Each 2-mL vial of lyophilized MenACWY-TT DP contains the content from 0.5 mL of (b) (4) of each conjugate in (b) (4) trometamol buffer, (b) (4) sucrose, pH (b) (4)

Reviewer Comment (LP): I calculate the final contents of each lyophilized vial to be (b) (4) of each (b) (4) trometamol, (b) (4) sucrose, and (b) (4) NaCl.

3.2.P.2.2.1 Formulation Development

GSK developed and commercialized the MenACWY-TT vaccine (NIMENRIX), receiving approval in EU in 2012. Pfizer acquired NIMENRIX from GSK in 2015. The MenACWY-TT DP component has the same formulation as NIMENRIX. However, whereas NIMENRIX (b) (4) MenACWY-TT DP is reconstituted with a solution containing (b) (4)-MenB DP. Pfizer's development study consisted of formulating DP at target and in (b) (4) and (b) (4) levels of sucrose (b) (4) (b) (4) and pH (b) (4) for a total of (b) (4) conditions. After lyophilization, they stored the test vials for (b) (4) respectively, and performed stability testing in the (b) (4). All acceptance criteria were met and there was very little change in any of the assayed variables.

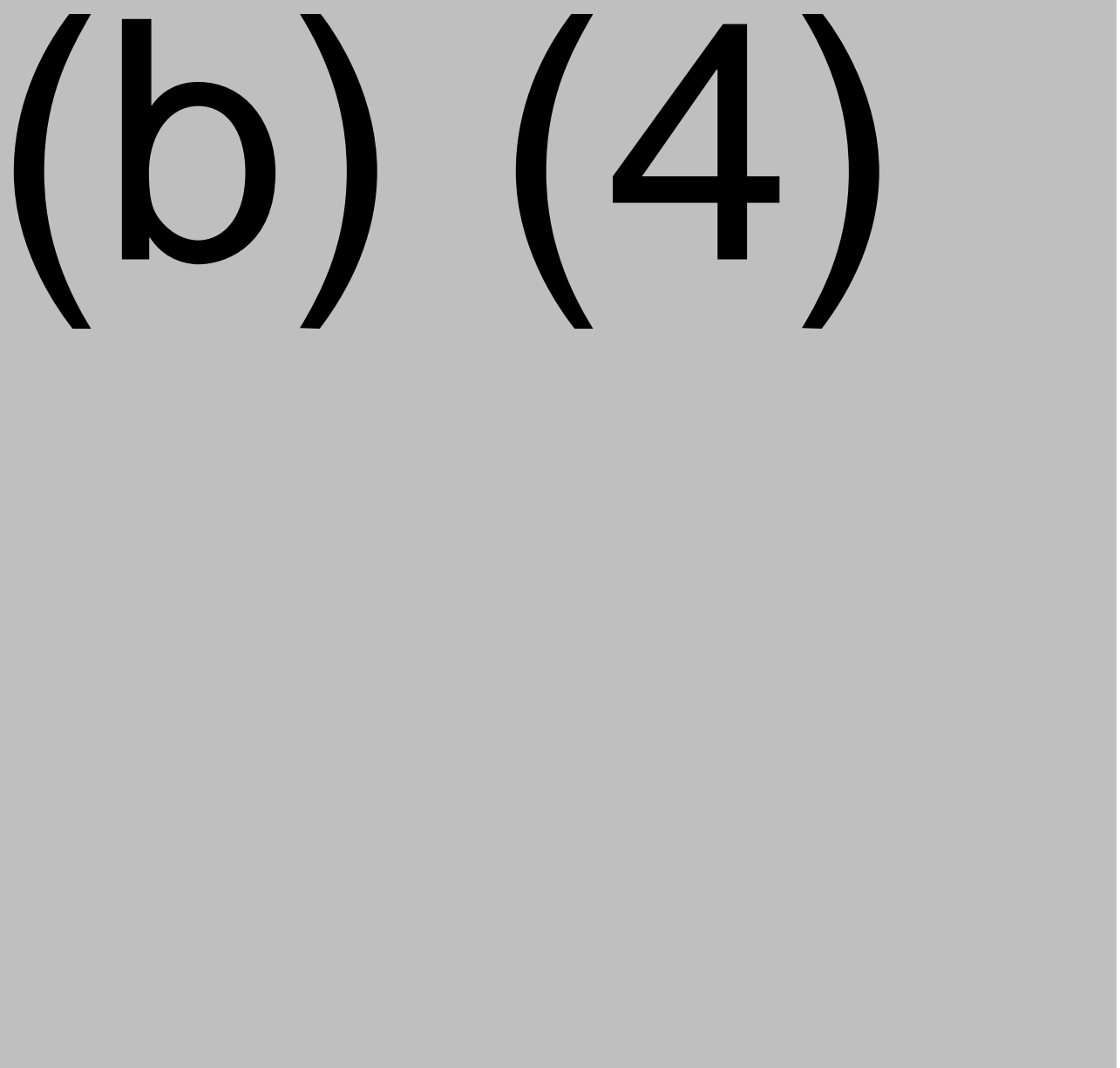
3.2.P.2.2.2 Overages

The MenACWY-TT DP has a (b) (4) prior to lyophilization in order to guarantee an effective injectable dose.

3.2.P.2.2.3 Physicochemical and Biological Properties

The MenACWY-TT DP is presented as a 2 mL vial as a lyophilized cake or powder.

3.2.P.2.3 Manufacturing Process Development



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

(b) (4)

3.2.P.2.4 Container Closure System (CCS)

Pfizer fills the MenACWY-TT DP component into 2-mL Type ^{(b) (4)} borosilicate glass vials manufactured by (b) (4) and

sterilized by (b) (4). They seal the vials with (b) (4) bromobutyl rubber stoppers followed by aluminum crimp seals with tamper-evident polypropylene flip off caps. Pfizer performed extractables studies on the stoppers using water at different (b) (4) for (b) (4) in the (b) (4). (b) (4) Under (b) (4) (b) (4) were the most abundant compounds observed. Pfizer is currently performing leachables studies on (b) (4) DP component lots stored (b) (4) at (b) (4) for (b) (4). (b) (4) At the (b) (4) timepoint, they did not detect the (b) (4) aforementioned compounds by (b) (4) nor did they detect any unexpected leachable compounds in amounts greater than the (b) (4) threshold amount. Please see section 3.2.P.7 for more about information about the CCS.

Reviewer Comment (LP): I sent an IR 14 April 2023 requesting the E&L report for the CCS and not just the summary. Pfizer sent report INX10557716 which matched their summary data appropriately. The full review of the response is under 3.2.P.2.4 in the (b) (4)-MnB DP section under 05May23-IR, Question 1.

3.2.P.2.5 Microbiological Attributes

Pfizer supplies MenACWY-TT DP as a single-use sterile lyophilized powder with no preservatives. They summarized their sterile testing methods, then described the (b) (4) (b) (4) test used to assay the CCS and verify the (b) (4) limits during the container sealing process. The (b) (4) test consisted of (b) (4) (b) (4) Pfizer tested (b) (4) capped using high (b) (4) and low (b) (4) settings. No vials were rejected due to leakage.

3.2.P.2.6 Compatibility

Compatibility with the MnB DP is described under the MenABCWY DP section, below.

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

LP: Pfizer characterized each step of the manufacturing process to ensure sterility, comparability to batches made at GSK and on different filling lines and lyophilizers, and acceptable E&L. Pfizer initially provided only a summary of the E&L studies, so I sent an IR requesting the report. Pfizer complied in their response under STN 125770/0.15. The summarized data reflect those in the report. Please see 05May23-IR-Question 1 under (b) (4)-MnB DP section 3.2.P.2.4 for more information. I find the information in this section acceptable as submitted.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

(b) (4)

(b) (4)

3.2.P.3.2 Batch Formula

The target DP component batch size is (b) (4) with (b) (4) of each conjugate in a buffer of (b) (4) trometamol, (b) (4) sucrose. The lyophilizer (b) (4) may vary between (b) (4) to (b) (4) vials.

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

LP: I find the information in this section acceptable as submitted.

3.2.P.3.3 Description of Manufacturing Process

(b) (4)

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

supplier. They did not list any specifications, but state they comply with the current version of (b) (4)

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

Not applicable.

3.2.P.4.4 Justification of Specifications

Not applicable.

3.2.P.4.5 Excipients of Human or Animal Origin

These are discussed under 3.2.A

3.2.P.4.6 Novel Excipient

Not applicable.

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

LP: All excipients for MenACWY-TT are (b) (4). I find the information in this section acceptable as submitted.

(b) (4)

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

(b) (4)

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

LP: Pfizer adequately resolved two deficiencies in their 05 May 2023 responses to our IRs. The acceptance criteria are appropriate to control the critical attributes of the MenACWY-TT DP.

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures (LP)

Pfizer's analytical procedures for the MenACWY-TT DP are listed in section 3.2.P.5.1, above.

In a December 8, 2022 meeting with DBSQC, the review team agreed that DBPAP (LP) would be responsible for reviewing the validation of the (b) (4) assay, while DBSQC would review the other procedures. Please refer to the DBSQC review memo for information on the assays not described below.

(b) (4)

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

(b) (4)

3.2.P.7 Container Closure System

Pfizer fills the MenACWY-TT DP component into 2-mL Type ^{(b) (4)} borosilicate glass vials manufactured by (b) (4)

(b) (4) and sterilized by (b) (4). They seal the vials with (b) (4)

(b) (4) bromobutyl-rubber stoppers manufactured by (b) (4)

(b) (4) followed by aluminum crimp seals with tamper-evident polypropylene flip off caps manufactured by (b) (4)

(b) (4) Quality control (QC) testing of vials and stoppers consists of visual identification and acceptance of the manufacturer's certification for each lot and dimension checks on at least (b) (4). QC testing of the crimp seals consists of visual and physical inspection of each lot. This file contains a description and drawings of the dimensions. E&L studies are described above under 3.2.P.2.4 *Container closure system*. Vial and stopper depyrogenation and sterilization are discussed under 3.2.P.3.5 *Process Validation* and container closure integrity testing is described under 3.2.P.2.5 *Microbiological Attributes*.

Pfizer does not ship the vials since final packaging occurs in the same location (b) (4) the ACWY-TT DP is manufactured.

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

LP: I find the information on the materials and manufactures in this section acceptable as submitted.

3.2.P.8 Stability

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

Per an agreement with CBER on 11 February 2022 in a Type B CMC pre-BLA written response, Pfizer submitted long-term stability data to support an 18-month shelf life at 2–8°C in glass vials within 30 days of this initial BLA submission on 17 November 2022. Both the initial and later stability data submissions (125770/0.1) are reviewed here.

Pfizer is currently conducting stability studies on (b) (4) lots, (b) (4) of which were (b) (4) for the lyophilizer studies. Pfizer's stability studies are as follows:

- *Long term:* 2–8°C to (b) (4) months. Currently, (b) (4) lot has data to 24 months, (b) (4) lots have data to 18 months, (b) (4) lots have 12 months of data, and (b) (4) lots have 3 months of data.
- *Accelerated:* (b) (4) for 6 months. All lots have completed these studies except for the most recent (b) (4) with 3 months of submitted data.
- (b) (4) for (b) (4) month. The (b) (4) study Pfizer did is complete.
- (b) (4) The study is complete.
- (b) (4) followed by long term storage. Three lots currently have 12 months of data.
- (b) (4) followed by long-term storage. Pfizer used (b) (4) for this study and currently has 12 months of data.

The DP exhibited no significant changes under any of the storage conditions. DP under long-term conditions had (b) (4) after the first datapoint. Reconstitution time tended to (b) (4) after the first datapoint. The data supports the proposed shelf-life.

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

Pfizer commits to enrolling at (b) (4) MenACWY-TT DP component (b) (4) in the commercial stability program at the long-term storage condition. They will monitor appearance before and after reconstitution, (b) (4) container closure integrity, (b) (4) pH, PS content, reconstitution time, particulates, and (b) (4) at 0, 12, 18, 24, (b) (4) months. Sterility will be assessed at time zero and end of shelf life.

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

LP: The data support the proposed 18-month shelf-life for lyophilized MenACWY-TT DP component at 2–8°C. I find the information in this section acceptable as submitted.

Reviewed by LP

3.2.P DRUG PRODUCT MenABCWY Liquid

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

Pfizer has developed MenABCWY DP for the prevention of invasive meningococcal disease due to *N. meningitidis* serogroups A, B, C, W, and Y. They package the MenABCWY vaccine DP as a combination product comprising lyophilized MenACWY-TT in a 2-mL Type ^{(b) (4)} glass vial, a (b) (4) vial adapter, and ^{(b) (4)}-MnB in solution in a pre-filled 1.0-mL syringe. Customers reconstitute the vaccine prior to use by utilizing the vial adaptor to inject ^{(b) (4)}-MnB into the vial containing lyophilized MenACWY-TT. After mixing the two components by gently swirling, the user withdraws the extractable content from the vial using the syringe. The final 0.5-mL dose contains 60 µg each of (b) (4) subfamily A and B proteins; 5 µg each of PS serotypes A, C, W, and Y; and ~44 µg of TT at pH 6.0. The vaccine also contains L-Histidine for pH control, trometamol (also called tromethamine) as a buffering component, sucrose and aluminum phosphate as stabilizers, PS80 as a surfactant, NaCl for (b) (4) water for injection, and possibly (b) (4) or (b) (4) as pH titrants. There are no preservatives. Overages are described under the separate DP components. Pfizer has defined the shelf life of the MenACWY-TT component as 'Minimum of' 18 months at 2–8°C,' and that of the ^{(b) (4)}-MnB DP component as 'Minimum of' 24 months at 2–8°C.' The shelf life of the combination product is the shortest shelf life of either DP component or of the vial adapter lot in the kit, when stored at 2–8°C.

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

- ^{(b) (4)}-MnB DP, (b) (4) in a 1-mL pre-filled syringe
- MenACWY-TT DP, lyophilized, in a 2-mL vial

3.2.P.2.1.1 Drug Substance

(b) (4)

(4)

3.2.P.2.1.2 Excipients

Table 3.2.P.2.1-1 lists the following excipients:

- Trometamol (Tris base), (b) (4) to provide pH control in the MenACWY-TT DP
- Sucrose, (b) (4), as a cryoprotectant and stabilizer (b) (4) of the MenACWY-TT DP
- AlPO_4 (b) (4) to stabilize the subfamily A and B proteins
- PS80, (b) (4) to prevent adsorption of protein to contact surfaces
- L-Histidine (b) (4), pH (b) (4) to provide pH control and ensure binding to AlPO_4
- NaCl (b) (4) to provide (b) (4) suitable for injection (updated to (b) (4) please see 05May23-IR, Question 6, below)
- WFI, diluent to make up final volume of the (b) (4) MnB DP component

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

(b) (4)

3.2.P.2.2.3 Physicochemical and Biological Properties

Please refer to the separate DP component sections, above.

3.2.P.2.2.4 Confirmation of 0.5 mL deliverable volume of MenABCWY Vaccine

(b) (4)

3.2.P.2.3 Manufacturing Process Development

Pfizer states the preparation of the final vaccine is performed prior to administration and does not require additional process development studies.

(b) (4)

3.2.P.2.4 Container Closure System

Pfizer tested the container to verify:

- Volume of injection (see 3.2.P.2.2.4)
- (b) (4)
- Functional attributes post-transportation
- That the adaptor did not become dislodged and leak during dose preparation or administration

(b) (4) testing included measuring (b) (4) (b) (4) in different syringes with different adapters. All values were similar and met the acceptance criteria. Pfizer also assessed device and usability-related risks and complaints acquired during clinical studies. Table 3.2.P.2.4-4 lists the required tasks to administer the vaccine, potential use errors and control measures. E&L information was under the individual DP component sections.

3.2.P.2.5 Microbiological Attributes

Please see the drug product component sections.

3.2.P.2.6 Compatibility

Pfizer tested the stability of (b) (4) reconstituted lots up to (b) (4) (MnB) and (MenACWY-TT) months old. They held the individual components for (b) (4) at (b) (4) (b) (4) prior to reconstitution and then evaluated them (b) (4) after reconstitution at (b) (4). All values were within the acceptance values except for a loss in (b) (4) which dropped to (b) (4) (below the (b) (4) acceptance criterion) after (b) (4) in (b) (4) mix due to minor degradation. Pfizer states the product is meant for immediate use after a recommended room-temperature equilibration so the degradation after 24 hours should not be an issue.

Pfizer did not assay to determine if the T0 point met the stability acceptance criterion of (b) (4) for each PS. They only assayed to show that the change over (b) (4) hours was (b) (4) of the T0 value. The T0 value for MenC was (b) (4) and for MenA and Y was (b) (4) when MenACWY-TT lot (b) (4) was mixed with (b) (4)-MnB lot (b) (4). The MenY value for MenACWY-TT lot (b) (4) (aged (b) (4) mixed with (b) (4)-MnB lot (b) (4) (aged (b) (4) was also right at the border of acceptable (b) (4). I sent an IR asking Pfizer to justify their proposed dating period (see 05May23-IR-Question 7).

Information Requests

05May23-IR

[Sent by CBER 24 April 2023. Response received 05 May 2023 (STN 125770/0.15)]

CBER Question 6

In MenABCWY DP Section 3.2.P.2-1 Pharmaceutical Development – Introduction, Table 3.2.P.2-1 on page 6, you indicate that the formulated vaccine contains (b) (4) sodium chloride, yet in Section 3.2.P.2.1, Components of the DP, Table 3.2.P.2.1-1 MenABCWY Drug Product – Excipients, you list the amount as (b) (4). Please clarify the discrepancy for NaCl content in these two tables and provide an updated table as necessary.

Pfizer's Response to Question 6

Pfizer indicated the NaCl concentration listed in Table 3.2.P.2.-1 (b) (4) was a typographical error and corrected it to say (b) (4) NaCl.

Reviewer Comment (LP): *I was expecting Pfizer to change the table to indicate (b) (4) NaCl to account for the NaCl present in the lyophilized MenACWY-TT DP. Therefore, on 13 July 2023 we sent an additional IR:*

28July23-IR

[Sent by CBER 13 July 2023. Response received 28 July 2023 (STN 125770/0.26)]

CBER Question 3

In your response to question 6 in 125770/0.15 (05 May 2023), you state that the MenABCWY DP contains (b) (4) NaCl. Considering there are approximately (b) (4) of NaCl in the lyophilized MenACWY DP component due to the (b) (4) (b) (4) NaCl in each conjugate (b) (4) and that the MnB DP component contains (b) (4) (b) (4) NaCl by itself, please explain how you calculated that the final MenABCWY DP has only (b) (4) NaCl.

Pfizer's Response to Question 3

Pfizer sent in tables calculating the concentration of NaCl in typical (b) (4) and worst-case (b) (4) scenarios after dilution of the PS-TT (b) (4). After combination with (b) (4)-MnB, they calculated the final concentration would be (b) (4) to (b) (4) NaCl per dose based on those values. They updated relevant sections to reflect the typical case of (b) (4) NaCl per dose.

Reviewer's Comment (LP): *Pfizer corrected the documents to reflect what is in the final DP. This is acceptable.*

05May23-IR

[Sent by CBER 24 April 2023. Response received 05 May 2023 (STN 125770/0.15)]

CBER Question 7

In 3.2.P.2.6 Compatibility [MenABCWY], MenACWY-TT (aged (b) (4)) had (b) (4) values near or at your acceptance criterion of (b) (4) when mixed with (b) (4)-MnB aged (b) (4) (under T0 in Tables 3.2.P.2.6-4 and (b) (4)). Your proposed shelf life for MenABCWY is based on the shortest expiry date of the components, i.e., up to (b) (4). A low MenACWY-TT (b) (4) value at (b) (4) indicates this parameter may fall below your acceptance criterion for the reconstituted DP prior to (b) (4). In addition, your expiry dating is based on the behavior of the DP when reconstituted in saline. The difference in the antigenicity data when DP is reconstituted in MenB suggest that saline may not adequately reflect the conditions in the final reconstituted product. Please justify your proposed dating period for MenABCWY.

Pfizer's Response to Question 7

Pfizer implicated assay variability as the reason for the (b) (4) values for aged lots and stated that there is no consistent (b) (4) due to the component's age. They submitted Table 1 in the response to the IR with (b) (4) aged lot combinations, one of which is also in table 3.2.P.2.6-1. In the new table the lots (b) (4) are (b) (4) older (b) (4) respectively). All values for all serotypes are greater than (b) (4).

Reviewer Comment (LP): Pfizer's explanation is reasonable and although only (b) (4) of the batch pairs in the original table 3.2.P.2.6-1 is in the submitted table 1 (b) (4) it is the oldest pair, and the (b) (4) that had a value lower than the acceptance criterion. This is acceptable.

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

LP: Pfizer optimized the (b) (4)-MnB DP component to ensure the correct amount of final DP is administered upon injection. They demonstrated the MenACWY-TT and (b) (4) MnB components are compatible when mixed and verified the shelf-life was appropriate in response to my IR, 05May23-IR Question 7. Finally, they incorporated the NaCl remaining in the conjugate (b) (4) into the calculation of NaCl in the final DP in response to 05May23-IR Question 6 and 28Jul23-IR Question 3 above. This is acceptable.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

(b) (4)

(b) (4)

3.2.P.3.2 Batch Formula

See 3.2.P.3.2 under the DP components.

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

LP: I find the information in this section acceptable as submitted.

3.2.P.3.3 Description of Manufacturing Process

(b) (4)

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

(b) (4)

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

LP: Pfizer did extensive testing on shipping conditions. I find the information supportive of the proposed MenABCWY DP shipping conditions and acceptable as submitted.

3.2.P.4 Control of Excipients

Please refer to DP component sections, above.

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

LP: The MenABCWY DP does not contain any additional excipients beyond those described under the MenACWY-TT and MnB Bivalent (b) (4) DP.

3.2.P.5 Control of Drug Product

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

Pfizer has established four attributes for the MenABCWY DP on release and stability:

(b) (4)



- Volume of injection of (b) (4) 0.5 mL.

(b) (4)

Appearance

Pfizer established the analytical procedure and acceptance criterion for appearance early in development.

(b) (4)



Volume of injection

Pfizer chose a volume of injection of (b) (4) 0.5 mL based on the required MenABCWY dosage.

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

LP: Pfizer's chosen tests to assay the physical and antigenic properties of the reconstituted DP are appropriate.

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

In a December 8, 2022 meeting with DBSQC, the review team agreed that DBPAP (LP) would be responsible for reviewing the validation of the (b) (4) assay, while DBSQC would review the other procedures. Please refer to the DBSQC review memo for information on the assays not described below.

(b) (4)

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

(b) (4)

3.2.P.7 Container Closure System

Please see the separate DP component sections, above, for a description of the vials and syringes. Pfizer uses a sterile polycarbonate vial adaptor with a luer lock connection on one side and a spike/snap-on connection on the other side. The adaptor spike is meant to puncture the vial septum as the adapter is attached. The adaptors are sterile packaged individually.

Reviewer Comment (LP): Drawings and E&L for the syringe and vial components are included under the DP component modules, but Pfizer did not provide a drawing or extractables and leachables information for the vial adapter. Pfizer did include certificates of compliance/analysis for the vial adapters from (b) (4) (b) (4) tests their adapters for (b) (4) while (b) (4) does not mention it. Pfizer does not consider the vial adaptor as part of the container closure system and the adaptors have 510(k) registrations. (See 05May23-IR-Question 2 below). This is acceptable.

Information Request

05May23-IR

[Sent by CBER 24 April 2023. Response received 05 May 2023 (STN 125770/0.15)]

CBER Question 2

In Section 3.2.P.7 for MenACWY-TT DP and MnB DP, you provided representative drawings of your container closure systems. However, while you describe your vial adapter in Section 3.2.P.7.2 (MenABCWY DP), you did not provide representative drawings of the vial adapter, nor did you provide dimensional information. Per Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics, applicants should provide dimensional information for their container closure systems, which is frequently part of schematic drawings. Please provide dimensional information and representative drawings for your vial adapter.

Pfizer's Response to Question 2:

Pfizer states that the 13 mm vial adapter is not defined as a container closure system and that the information regarding the adapters is in the manufacturer's respective 510(k) registrations, therefore what they submitted already meets the industry guidelines.

Reviewer Comment (LP): *As the vial adapter is not part of the CCS, a schematic is not required.*

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

LP: The container closure system and reference materials are the same as those used for the DP components. The only addition is the vial adapter, for which the manufacturers have 510(k) registrations, and is not part of the CCS. This is acceptable.

3.2.P.8 Stability**3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data**

Pfizer has not conducted any formal stability studies on the reconstituted MenABCWY DP. They propose a shelf life, when stored at 2–8°C, as the shorter of the two DP components. The proposed shelf life for MenACWY-TT is 18 months and that of the MnB component is 24 months.

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

Pfizer proposes enroll a minimum of (b) (4) MenABCWY DP lot, post-approval, in the stability program (b) (4) and test the DP for appearance (after reconstitution), protein (total), (b) (4), and volume of injection every (b) (4) to the end of the shortest shelf life of the individual DP component, although in Table 3.2.P.8.2-1, they propose a test interval up to (b) (4)

Although they did not submit stability data on the reconstituted product, Pfizer did test (b) (4) combinations of batches aged from (b) (4) under 3.2.P.2.6 *Compatibility*.

They assayed reconstitution time, appearance, pH, (b) (4), protein (total), (b) (4) purity, (b) (4) and (b) (4) content, which is a more extensive set of tests than they propose for stability which are appearance, protein (total), (b) (4) and volume of injection. The reconstituted lot with the oldest components (b) (4) for MenACWY-TT and (b) (4) for MnB had (b) (4) (b) (4) for MenACWY, all at or below the acceptance criterion of (b) (4). The other batches for MenACWY-TT were (b) (4) and met the criterion, although MenY in batch (b) (4) had a value of (b) (4). Pfizer claims the low values were due to assay variability (see 05May23-IR-Question 7 under 3.2.P.2.6, above).

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

LP: Pfizer addressed our IR regarding the MenACWY (b) (4) values decreasing upon reconstitution, as discussed under Module 3.2.P.2.6, above. The proposed shelf life of MenABCWY as the shorter of the two DP components is acceptable.

Reviewed by JK and LP

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

We defer to DMPQ for review of this module.

3.2.A.2 Adventitious Agents Safety Evaluation

The applicant lists human or animal-derived materials in Tables 3.S.A.2-1 and -2 for the MnB (b) (4) and DP components and in Tables 3.2.A.2-3 and -4 for the MenACWY-TT (b) (4) components. They state all other materials are of synthetic and/or nonanimal biological origin. The applicant states that the main theoretical risk associated with these materials is contamination of the product with (b) (4) agents and then describes how they have worked with their suppliers, the U.S. FDA, and other agencies worldwide to collect the most up-to-date information and keep abreast of changes in compliance expectations.

In summary, for the MnB proteins, they use:

- (b) (4) or (b) (4) of (b) (4) from (b) (4) sourced from (b) (4) (b) (4) and collected under the same conditions as that deemed suitable for human consumption. This component is used in (b) (4)
- Several consumables which contain traces of (b) (4) derived from (b) (4) (b) (4). These are: the container closure (b) (4) (b) (4) vials for (b) (4) and DP containers, (b) (4) used throughout (b) (4) and DP manufacture, the (b) (4) for DP manufacture, and the syringe cap and plunger stopper used with the syringes. Most materials have (b) (4) sourced from the (b) (4) although the source for the (b) (4) are unknown. The applicant states the

consumables are unlikely to be infectious due to the rigorous conditions under which the materials used to make them are processed and confirms the (b) (4) derivatives are compliant with the (b) (4) Note for Guidance, Section 6.4.

The materials of animal origin the sponsor uses for the manufacture of the MenACWY-TT DP component are:

(b) (4)

Pfizer sources both materials from healthy (b) (4) animals in (b) (4) under the same conditions as milk collected for human consumption.

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

LP and JK: We reviewed Pfizer's evaluation of its overall control strategy to mitigate risks of endogenous and exogenous adventitious agents. The control strategy is acceptable. No deficiencies were found.

3.2.A.3 Novel Excipients

Not applicable.

Reviewed by JK and LP

3.2.R Regional Information (USA)

□ Executed Batch Records

Pfizer submitted a total of (b) (4) executed batch records for the (b) (4). These included, in both Swedish and English, (b) (4) and (b) (4) (MnB-B) used to produce the (b) (4)-MnB process validation lot (b) (4). They submitted batch records for (b) (4)

(b) (4) whose batch record they also provided. They are all listed in Table 3.2.R.1.S.1-2 in the document 3.2.R.1.2.1 *Batch Record Summary Table – Drug Substance*. These batches were used in process validation and stability studies. In addition, they submitted the (b) (4) (b) (4) batch records for TT (b) (4)

Pfizer submitted a total of (b) (4) executed batch records for the DP components. For the MnB DP component, they submitted the record for preparation of the buffer (b) (4) formulation filling (b) (4) and inspection and (b) (4) packaging (b) (4). They also included a representative record for manufacture of the aluminum phosphate suspension (b) (4). For the MenACWY-TT DP (b) (4) a confirmatory lot used for stability studies, they submitted the original Dutch and English translations of batch records for preparation of buffer formulation (b) (4) filling, lyophilization and final stoppering, sealing, and capping of lyophilized vials (b) (4) inspection and (b) (4) packaging (b) (4)

Reviewer Comment (LP): Pfizer did not provide a batch record for the final MenABCWY DP, nor any master batch records. We sent the following information request on 13 July 2023:

Information Request

28-July-23-IR

[Sent by CBER 13 July 2023. Response received 28 July 2023 (STN 125770/0.26)]

CBER Question 4

You submitted executed batch records for the (b) (4) DP components in section 3.2.R but did not submit an executed batch record for the MenABCWY DP or master batch records for any part of your manufacturing process. Please submit the following, or indicate where they can be found in your submission, so that we can complete your review:

1. Executed batch record for MenABCWY DP.
2. Master batch records for all aspects of your manufacturing process.

Pfizer's response to Question 4

1. Pfizer did not send in a master or executed batch record for MenABCWY. They stated, "the manufacturing process of MenABCWY DP only includes assembly, labeling and packaging," and referred to section 3.2.P.3.5 *Qualification of assembly, labeling, and packaging [MenABCWY]* which contains the process steps and a summary of the completed qualification.
2. Pfizer only submitted the master batch records (MBRs) for the MnB DP buffer, formulation, filling, inspection, and AlPO₄ suspension because the executed batch records (EBRs) were generated from the electronic batch record system. They stated the other EBRs are representative of the current commercial master records with no major changes. They also submitted the (b) (4) EBRs which were inadvertently omitted from the initial submission.

Reviewer Comment (LP):

I asked the DMPQ reviewer if the batch records for MenABCWY were required. They responded that they do not feel that these are needed, since "Guidance for Industry: Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product" states they are only required for drug substances, and since the facility in question (b) (4) has an acceptable compliance history. Therefore, the applicant's response is acceptable.

Per "Guidance for Industry, Providing Regulatory Submissions to CBER in Electronic Format – Biologics Marketing Applications" on page 19, it says each EBR should be provided in a PDF file. It does not mention MBRs. Since there have been no major changes to the MBRs since the submitted EBRs were

recorded and the guidance refers only to EBRs, I find submission of only the EBRs acceptable.

❑ **Method Validation Package**

The method validation information included in the section was reviewed along with validation summaries presented in Sections 3.2.S.2.5 *Process Validation and/or Evaluation* (b) (4) 3.2.S.4.3 *Validation of Analytical Procedures* (b) (4), 3.2.P.3.5 *Process Validation and/or Evaluation* (DP), and 3.2.P.5.3 *Validation of Analytical Procedures* (DP).

❑ **Combination Products**

Pfizer provided a summary of the device quality system regulation sub-system policy/procedures for the combination product in 3.2.R 21 *CFR Part 4 Description*. We defer review of this section to the Device Reviewer.

Overall Reviewer's Assessment of Combination Products Section:

N/A

❑ **Comparability Protocols**

(b) (4)

(b) (4)

Other eCTD Modules

Reviewed by LP

Module 1

A. Environmental Assessment or Claim of Categorical Exclusion

A claim of categorical exclusion has been submitted under **21 CFR 25.31(c)**. FDA concludes that this product occurs naturally in the environment, and approval of this BLA supplement does not significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment, and no extraordinary circumstances exist. The categorical exclusion claim is accepted.

B. Reference Product Designation Request

The applicant filed a claim of exclusivity on October 21, 2022, claiming there are no licensed biological products that are structurally related to the PENBRAYA vaccine for which they or one of their affiliates, licensors, predecessors in interest, or related entities is the current or previous license holder. They believe that PENBRAYA is not

structurally related to TRUMENBA because the licensure of PENBRAYA “constitutes the first licensure of the components relating to Nimenrix (Meningococcal Group A, C, W-135 and Y Conjugate Vaccine), with TT as the protein carrier (MenACWY-TT), which is more than a structural modification to TRUMENBA.” We disagreed and sent an Information Request to the applicant on May 31, 2023. The applicant responded on June 12, 2023.

Information Request

12Jun23-IR

[Sent by CBER 31 May 2023. Response received 12 June 2023 (STN 125770/0.20)]

We refer to your request submitted and received on October 21, 2022, regarding exclusivity. In order to assist Food and Drug Administration (FDA) in evaluating the date of first licensure as described in section 351(k)(7)(C) of the PHS Act for Neisseria meningitidis Group A, B, C, W, and Y Vaccine [MenABCWY], we have the following comments:

Regarding your claim for product exclusivity in Section 1.3.5.3, you state in section B that “there are no licensed biological products that are structurally related to (b) (4) (Neisseria meningitidis Group A, B, C, W, and Y [MenABCWY])” and in footnote 1, “that (b) (4) is not structurally related to TRUMENBA® because, among other things, the licensure of (b) (4) constitutes the “first licensure” of the components relating to NIMENRIX® (Meningococcal Group A, C, W-135 and Y Conjugate Vaccine), with tetanus toxoid (TT) as the protein carrier (MenACWY-TT), which is more than a structural modification to TRUMENBA.” However as described in the 2014 Guidance for Industry (Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act) you should include all products that share any of the same principal molecular structural features of the product being considered, but generally can be limited to products that affect the same molecular target. As Trumenba shares some of the same principle molecular structure features and targets as (b) (4) we do not agree with your assertion that Trumenba is not related.

- 1. Please submit a list of all licensed biological products that are structurally related and/or that share some of the same principal molecular structural features to the biological product that is the subject of the 351(a) application being considered. This list should include all products that share any of the same principal molecular structural features of the biological product being considered, but generally can be limited to products that affect the same molecular target. Of those licensed biological products identified this list, please identify the products for which you or one of your affiliates, including any licensors, predecessors in interest, successors in interest, or related entities are the current or previous license holder.*

2. *Based on our advice, please revise your exclusivity claim and include a list of all licensed biological products that are structurally related and/or that share some of the same principal molecular structural features to the biological product that is the subject of the 351(a) application being considered. If your assessment results in the conclusion that no products that have the same molecular target or share some of the same principal molecular structural features have been licensed, please provide an adequate justification to support the assertion that there are no previously licensed products that are relevant for purposes of determining the date of first licensure.*
3. *Please describe the structural differences between the biological product being considered and any products identified in item 2 above. For protein products, this should include, but is not limited to, changes in amino acid sequence, differences due to post-translational events, infidelity of translation or transcription, differences in glycosylation patterns or tertiary structure, and differences in biological activities.*
4. *Please provide evidence of the change in safety, purity, and/or potency between the proposed product and any products identified in item 2 above.*

Response to the Exclusivity IR

1. Pfizer acknowledged that Trumenba is structurally related to the corresponding (b) (4) components of PENBRAYA. However, they also state that PENBRAYA will constitute the “first licensure” of the components related to NIMENRIX with tetanus toxoid (TT) as the protein carrier (MenACWY-TT).
2. Pfizer provided an updated Exclusivity Claim in Module 1.3.5.3.
3. Pfizer cited Sections 3.2.S.3.1 of the respective (b) (4) as the locations in the eCTD where one can find the structures serogroups A, C, W, and Y polysaccharides used to manufacture the conjugate vaccines. They also stated that the chemical structures for serogroups A, C, W, and Y in PENBRAYA are “chemically and antigenically (i.e., functionally) unique” from the antigens in TRUMENBA. The A, C, W, and Y antigens are polysaccharides that are each individually conjugated to TT; polysaccharides are chemically distinct from the antigens in TRUMENBA, which are protein subunits. Additionally, combining these four polysaccharide conjugates with the antigens in TRUMENBA creates a unique, pentavalent meningococcal vaccine. Because all antigens may interact in a manner that could affect immunogenicity, such as immune interference or immune enhancement, Pfizer states that the pentavalent formulation is an “entirely new vaccine composition in its own right.”
4. Pfizer stated that the combination of antigens in PENBRAYA elicits immune responses that TRUMENBA cannot as TRUMENBA does not contain

serogroup A, C, W, or Y antigens. Thus, Pfizer contends that the pentavalent MenACWY formulation provides additional coverage above that of TRUMENBA, which they state they have demonstrated in the clinical studies included in this BLA (summarized in Module 2.5 of the eCTD).

Reviewer Comment (LP): *PENBRAYA contains four polysaccharide conjugates, which are not found in TRUMENBA. The Pfizer product from which the MenACWY-TT component of PENBRAYA is based, NIMENRIX, is not licensed in the U.S. Therefore, we agree that there are no currently licensed products in the U.S. other than TRUMENBA that are structurally related to PENBRAYA.*

The addition of the four polysaccharide conjugates to PENBRAYA leads to an immune response that is notably different than that of TRUMENBA because the antigens allow for responses specific to different meningococcal serotypes not targeted by TRUMENBA. This is a change in potency.

Determination of Exclusivity

PENBRAYA includes the same bivalent recombinant lipidated factor H binding protein as TRUMENBA. However, PENBRAYA contains an additional four antigens, all of which are polysaccharides conjugated to TT. These four antigens are unique to PENBRAYA relative to TRUMENBA, and thus will elicit immune responses that TRUMENBA cannot. This is a change in potency relative to TRUMENBA. Additionally, while both TRUMENBA and PENBRAYA contain the same serotype B antigens, the combination of five antigens in PENBRAYA could functionally change the immune responses to the serotype B antigens common between the two products. Therefore, the pentavalent MenACWY PENBRAYA vaccine is unique relative to other U.S.-licensed products.

CBER's reference product determination board met on 28 September 2023 and concurred with our recommendation to grant exclusivity. Upon approval, the product will be designated as a reference product and the associated exclusivity periods will be based upon the first date of approval.

C. Labeling Review

Full Prescribing Information (PI)

Prescribing information in the package insert (PI) contains information about the dosage, form, and strength of PENBRAYA, a description of its contents, a summary of the clinical pharmacology supporting its indication and instructions for storage and handling. In brief, the PI indicates that PENBRAYA is a suspension for injection as a single 0.5-mL dose after reconstitution. The Lyophilized MenACWY component consists of *N. meningitidis* groups A, C, W and Y PS individually conjugated to TT. The MenB component is a sterile suspension composed of two recombinant fHbp protein variants from *N. meningitidis* group B representing subfamily A and B, respectively.

Vaccination with PENBRAYA induces the production of bactericidal antibodies specific to the capsular polysaccharides of *N. meningitidis* groups A, C, W, and Y and to the fHbp subfamily A and B variants of *N. meningitidis* group B. Bactericidal activity is derived from complement-mediated antibody-dependent killing of *N. meningitidis*.

PENBRAYA is supplied in cartons of 1, 5, and 10 packages. Each package contains 1 single-dose vial of Lyophilized MenACWY Component, 1 prefilled syringe of MenB Component, and 1 vial adapter. The Lyophilized MenACWY Component is reconstituted with the MenB Component to form a single dose of PENBRAYA.

Carton and Container Label:

The primary and secondary container cartons were reviewed, and the information provided corresponds with DP contents described in Section 3.2.P.1.1 “Description and Composition of the Drug Product”. This is acceptable. .

Modules 4 and 5

Analytical Procedures and Validation of Analytical Procedures for Assessment of Clinical and Animal Study Endpoints

Reviewed by KM

Module 4

Pfizer, in conjunction with GSK, from whom Pfizer acquired the rights to NIMENRIX, conducted a series of pre-clinical animal studies to independently evaluate the pharmacology and toxicology of the MenACWY (NIMENRIX) and MenB (TRUMENBA) components that comprise PENBRAYA. In addition to their submission to Module 4 of BLA 125770, many of the same reports were submitted in parallel to the individual (b) (4) for NIMENRIX and TRUMENBA, (b) (4) IND 13812, respectively. As each study was reviewed under (b) (4) I have included a list of the studies below.

Pharmacology Studies

Pfizer submitted the following study reports to Module 4.2.1.1:

- **20030028**, entitled “Comparison of the immunogenicity of polysaccharides [sic] (A,C,Y,W) and conjugates (PSA-TT, PSC, PSW, PSY) in a mouse model”
- **20040272**, entitled “Evaluation of the immunogenicity of MenA-TT conjugates produced with different conjugation methods in a mouse model”
- **20040340**, entitled “Evaluation of the immunogenicity of MenC-TT conjugates produced with different conjugation methods in a mouse model”
- **20060046**, entitled “Evaluation of the immunogenicity of different MenACWY(-TT) formulations in a mouse model”
- **20030275**, entitled “Preliminary immunogenicity study with the MenACWY-TT vaccines in female rabbits”

- (b) (4) -6001, entitled “Repeated-dose toxicity study with a MenA(AH)CWY-TT candidate vaccine administered intramuscularly (two times) in male and female rabbits”
- P6001, entitled “Complementary serological analysis performed on rabbit sera from repeated toxicity study P6001: (b) (4)”

Reviewer Comment (KM): *The studies demonstrated immunogenicity of the individual NIMENRIX and TRUMENBA components of PENBRAYA, with generation of functional antibody responses. In the case of TRUMENBA, the vaccine elicited cross-reactive antibodies that were capable of killing outbreak strains in human complement serum bactericidal assays (hSBAs) that expressed antigens heterologous to those present in TRUMENBA. While the applicant did not conduct any studies to investigate the immunogenicity of the combined PENBRAYA vaccine, internal discussions within the Center determined that the immunogenicity studies described were adequate for submission of BLA 125770 due to the ability to analyze any impact of MenACWY or MenB component interference in the context of the Phase 3 clinical studies.*

Toxicology Studies

The following documents were submitted to Module 4.2.3:

- (b) (4) **Report, Study V 8217**, entitled “Repeated-dose toxicity study with a MenACWY-TT Candidate Vaccine administered intramuscularly (five times) to male and female rabbits”
- **Serology Report for Study V8217**, entitled “Repeated-dose toxicity study with a MenA(AH)C(AH)WY-TT candidate vaccine administered intramuscularly (five times) in male and female rabbits, Serological Report”
- **RPT-60511, Ver. 2.0**, entitled “(b) (4) -263069 (b) (4) and AIPO₄ (b) (4) 136352: (b) (4) (1 Dose/2 Week Cycle) Intramuscular Toxicity Study in Rabbits (Protocol 05_0388)”
- **RPT-61777, Ver. 2.0**, entitled “(b) (4) -263069 (b) (4) and AIPO₄ (b) (4) 136352: (b) (4) (1 Dose/2 Week/Cycle) Intramuscular Toxicity Study in Rabbits (Protocol 05_0388) – Antibody Report”
- **RPT-74041, Ver. 2.0**, entitled “(b) (4) Vaccine and AIPO₄ (b) (4) 136352: Repeat (b) (4) (1 Dose/2 Week Cycle) Intramuscular Toxicity Study in Rabbits (Protocol 07_1434)”
- **RPT-75177, Ver. 1.0**, entitled “(b) (4) Vaccine and AIPO₄ (b) (4) 136352: Repeat (b) (4) (1 Dose/2 Week Cycle) Intramuscular Toxicity Study in Rabbits (Protocol 07_1434): Serology Report”
- **RPT-75947, Ver. 2.0**, entitled “Meningococcal B Vaccine (b) (4) : A Combined Intramuscular Fertility and Developmental Toxicity Study in Female Rabbits (Protocol 08_3574)”
- **RPT-79795, Ver. 1.0**, entitled “Meningococcal B Vaccine (b) (4) : A Combined Intramuscular Fertility and Developmental Toxicity Study in Female Rabbits (Protocol 08_3574): Serology Report”

- **RPT-63113, Ver. 1.1**, entitled “(b) (4)-263069 (b) (4) and AIPO₄ (b) (4)-136352): A Combined Intramuscular Fertility and Developmental Toxicity Study in Female Rabbits (b) (4) Protocol 05_2860)”
- **RPT-65095, Ver. 1.0**, entitled “(b) (4) 00031 – (b) (4)-263069 (b) (4) and AIPO₄ (b) (4)-136352): A Combined Intramuscular Fertility and Developmental Toxicity Study in Female Rabbits ((b) (4) Protocol 05_2860) – Antibody Report”

Reviewer Comment (KM): *The reports collectively described immunogenicity studies carried out in conjunction with single- and repeat-dose toxicity studies and gestational studies. Data demonstrated elicitation of anti-MenACWY and anti-MenB seroresponses upon immunization of (b) (4) rabbits with either NIMENRIX or TRUMENBA, respectively. For a more detailed description of the studies and their respective results, see the Toxicology Reviewer’s memo.*

Reviewed by KM
Module 5

For evaluation of immunogenicity endpoints in clinical studies C3511001, C3511004, and B1971057, Pfizer tested study participant serum samples using anti-MenB and anti-MenACWY hSBAs. All assays were performed using the same format. In the hSBAs

(b) (4)

Serological Assay Development

Anti-MenB hSBA

Pfizer originally submitted qualification and validation reports for the MenB hSBAs under IND 13812 and BLA 125549 in support of the accelerated approval of TRUMENBA, with review of the relevant documents under IND 13812 (Amendments 135, 144, 150, and 172) and BLA 125549/0. I subsequently verified suitability of the assays for use in assessing anti-MenB antibody responses upon review of additional documents submitted by Pfizer in support of confirmatory study B1971057, which was conducted as

required under the conditions of accelerated approval (see memos to IND 13812, Amendments 408 and 426, and BLA 125549/737). Pfizer submitted the MenB hSBA validation reports, which remained unchanged, to BLA 125770/0. The precision, linearity, and additional data presented in the reports confirmed the adequacy of the individual hSBAs in measuring functional anti-MenB antibody responses with the assay limits/ranges specified in the table below (where value indicates the reciprocal titer dilution; LOD, LLOQ, and ULOQ represent the limit of detection, the lower limit of quantitation, and the upper limit of quantitation, respectively).

Table 22: Assay limits and ranges for anti-MenB hSBAs

Strain	LOD	LLOQ	ULOQ	Range
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)				
(b) (4)				
(b) (4)				

Reviewer Comment (KM): All validation activities were performed by the Pfizer Vaccine Research group in (b) (4) which was also the site of clinical sample testing, demonstrating the ability of the on-site staff to conduct the hSBA procedure. LODs and LLOQs cited were supported by the data and were sufficiently low to permit interpretation of the primary immunogenicity endpoints of pivotal clinical studies C3511001 and C3511004, which included quantification of the proportion of participants with anti-MenB post-vaccination titers \geq LLOQ and the difference in the proportion of seroresponders, where a seroresponse is defined as: for a baseline titer (1) $<$ LOD, a titer (b) (4) or the LLOQ, whichever is higher, (2) \geq LOD and $<$ LLOQ, a titer (b) (4) LLOQ, and (3) \geq LLOQ, a titer (b) (4) the baseline titer.

Assays were also suitable for evaluation of secondary and exploratory endpoints in all studies (including study B1971057), as the majority of endpoints included assessment of the proportion of subjects achieving a certain threshold titer that was within the anti-MenB assay ranges (i.e., (b) (4) and \geq LLOQ). Likewise, the hSBAs were suitable for evaluation of endpoints that included titers $>$ ULOQs of the respective anti-MenB hSBAs (i.e., GMTs and proportion of seroresponders), as the hSBA protocol specifies that (b) (4) such that the final reported titer will be back-calculated from an endpoint titer falling within the assay range.

Anti-MenACWY hSBAs

To support the use of anti-MenACWY hSBAs in evaluation of serological data in clinical studies C351101, C351104, and B1971057, Pfizer first submitted qualification reports to IND 17319.24. The applicant subsequently submitted validation reports to IND 17319.110 on 03 November 2021.

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

(b) (4)

Assessment of IR Responses for Module 5

20Jan23-IR

[Sent by CBER 20 December 2022. Response received 20 January 2023 (STN 125770/0.4)]

CBER Question 1

In your submission, you provided supplemental validation reports VR-MVR-10020, Ver. 4.0, VR-MVR-10021, Ver. 3.0, and VR-MVR-10022, Ver. 4.0, describing studies conducted to assess (b) (4)

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

However, it is unclear if you conducted similar studies for (b) (4) (b) (4)

(b) (4) Please clarify whether you assessed the (b) (4)

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

rates were assessed, please submit the relevant validation report to BLA 125770 and IND 17319.

Pfizer's Response to Question 1

Pfizer indicated that they incorporated data assessing (b) (4)

(b) (4) (b) (4) (b) (4) (b) (4) validation report, document VR-MVR-10017, and demonstrated that an (b) (4) was acceptable.

Reviewer Comment (KM): *The response is acceptable.*

CBER Question 2

In Section 7.2.2 of the clinical study protocol for study B1971057, you stated that testing of samples in serum bactericidal assays (SBAs) was conducted at one or both of the following laboratories: (b) (4)

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

Additionally, in Module 16.1.10 of the Study Report Body Chapters for clinical studies C3511001 and C3511004, you state that primary sample testing was conducted at the site of the method validation studies, (b) (4)

(b) (4) with secondary testing conducted at the (b) (4)

However, it is unclear whether (a) the (b) (4)

(b) (4) laboratory is associated with the (b) (4)

(b) (4) laboratories, and (b) if method validation was conducted at both the

(b) (4) and the (b) (4)

(b) (4) Please clarify the site of clinical sample testing for each of the studies and whether a formal validation study was conducted at each facility. Please note that method validation must be performed at each of the sites of clinical sample testing to support serological data for licensure of the MenABCWY vaccine.

Pfizer's Response to Question 2

Pfizer clarified that the (b) (4) laboratory is the same laboratory as the (b) (4) (b) (4) Pfizer additionally confirmed that the anti-MenB and the anti-MenACWY hSBAs were performed at their respective sites of validation, the (b) (4) laboratories and the (b) (4) in (b) (4) (see memo section entitled "Serological Assay Development" for additional details).

Reviewer Comment (KM): *The response is acceptable.*

CBER Question 3

Upon review of the documents submitted to BLA 125770, we were unable to locate either (a) the SOP for the MenB and MenACWY SBA methods or (b) data to support stability of the MenB and MenACWY SBA methods from the period of assay validation through clinical sample testing. In order to facilitate our review, please submit the missing documents to BLA 125770 and IND 17319 as needed.

Pfizer's Response to Question 3

Pfizer submitted documents VR-TM-10291, Ver. 3.0, entitled "*Neisseria meningitidis* Serogroup B hSBA Performance Using (b) (4)" and VR-(b) (4)-10123, also labeled VR-TM-10243PPD, Ver. 4.2, entitled "*Neisseria meningitidis* Serogroups A, C, W, and Y (MenA, MenC, MenW, and MenY) Serum Bactericidal Assay Using Human Complement (hSBA) in (b) (4) Using a (b) (4) as requested. The documents described the same methodology as applied to all hSBAs, which was described in the memo section entitled, "Serological Assay Development."

Pfizer additionally provided data as requested to demonstrate stability of the hSBAs from the period of assay validation through the clinical testing period. The applicant explained that the performance of the anti-MenB and anti-MenACWY hSBAs is monitored using (b) (4) (b) (4)

Control graphs indicated the hSBA results were equivalent to the specification limits determined during baseline testing.

Reviewer Comment (KM): (b) (4) fell within the pre-defined specification limits throughout the clinical testing periods of studies C3511001, C3511004, and B1971057. However, the limits for some of the (b) (4) (b) (4) (b) (4) also appeared to be within their respective specification limits

(b) (4) throughout the clinical testing periods, though Pfizer's use of a (b) (4) inhibited the ability to ascertain if the defined limits were overly broad. In addition, the following aberrant data were noted: (b) (4)

(b) (4) increasing or decreasing above or below the specification limits directly after baseline testing, then returning to baseline (b) (4) towards the end of the clinical testing period.

Considering the anti-MenB hSBAs were validated between (b) (4) while the anti-MenACWY hSBAs were validated in (b) (4), it is likely that the greater variability observed in the anti-MenACWY (b) (4)

(b) (4) To confirm assay stability, however, further clarification regarding the specification limits was needed.

Additional information was requested in conjunction with a second IR conveyed to Pfizer in response to the submission to IND 17319.147:

09Feb23-IR

[Sent by CBER 10 January 2023. Response received 09 February 2023 (STN 125770/0.7)]

CBER Question 1

In Section 5.3 of the hSBA validation protocol #VR-MRP-10070, you describe the methods by which you defined lower and upper specification limits (LSL and USL, respectively) for each of the (b) (4)

(b) (4)

Pfizer's Response to Question 1

Pfizer provided documents detailing previous discussions with us regarding the method by which (b) (4) would be reported (i.e., (b) (4) confirming our agreement that (b) (4) would be reported for clinical studies, but that assays would be monitored using (b) (4) with specification limits defined according to (b) (4). Pfizer justified use of (b) (4) to calculate specification limits by stating that the approach was consistent with licensure of TRUMENBA and that (b) (4) are more sensitive to assay changes compared to (b) (4).

Reviewer Comment (KM): Consultation with the Statistical Reviewer confirmed the applicant's assertion regarding (b) (4). However, the possibility remained that the use of (b) (4) SDs instead of (b) (4) SDs was too broad and allowed for recording of imprecise data that should have been excluded. An examination of the impact of using (b) (4) vs. (b) (4) SDs for establishment of specification limits was warranted and requested in a subsequent IR (see 03Apr23-IR, below).

CBER Question 2

In Section 5.6.1 of document #VR-MRP-10070, you indicate that (b) (4), the (b) (4) utilized for (b) (4), was (b) (4).

(b) (4) (b) (4)
Although (b) (4) may constitute an appropriate (b) (4) (b) (4) (b) (4), the depletion process may also have unintentionally diminished levels of additional serum components, such as complement factors, that influence serum bactericidal activity. Because low-titer clinical samples (i.e., pre-immune sera or sera from low vaccine responders) will contain serum components and non-MenACWY IgG levels comparable to high-titer samples, accuracy at the low end of the hSBAs may only be demonstrated using mock samples that reflect these components as closely as possible. To confirm suitability of the (b) (4) (b) (4) as a (b) (4) please provide data from a subset of samples tested in parallel linearity experiments in the (b) (4) and an additional (b) (4) e.g., pre-immune serum that has been pre-screened to exhibit anti-MenACWY (b) (4). Please note that if comparability between the (b) (4) matrices cannot be demonstrated, linearity studies will need to be repeated in an appropriate (b) (4) to complete assay validation.

Pfizer's Response to Question 2

Pfizer responded that we previously concurred with the use of the (b) (4) (b) (4) for linearity studies supporting the licensure of TRUMENBA.

Reviewer Comment (KM): Review of the meeting notes provided confirmed Pfizer's assertion. The response is acceptable.

CBER Question 3

In documents VR-RGR-RS-10520, VR-RGR-RS-10498, VR-RGR-RS-10523, and VR-RGR-RS-10499, you provided graphs depicting the individual (b) (4) of the (b) (4) throughout the (b) (4) testing period, as assessed in accordance with the specification limit ranges calculated for each of the (b) (4). However, it is unclear from the graphs how many of the reported (b) (4) were outside of the (b) (4) variability margin that is considered acceptable for hSBAs. Please re-submit the graphs defining the (b) (4) variability margin, where you have highlighted (b) (4) changes in (b) (4) relative to the GMT.

Pfizer's Response to Question 3

Pfizer referred to their response to Comment 1, re-stating that the use of a (b) (4) specification limit was improper.

Reviewer Comment (KM): Although implementation of a (b) (4) specification limit for monitoring (b) (4) in the hSBAs would be advantageous, as the resultant (b) (4) would more closely reflect the variability inherent in the assay on a per-(b) (4) basis, the results produced using Pfizer's method vs. the proposed (b) (4) specification limit were largely comparable. When considered in accordance with previous discussions regarding control of hSBAs for licensure of TRUMENBA, I find the response acceptable.

CBER Question 4

In your response to CBER comment 1c, you state that you included document VR-SOP-LC-11208(b) (4) entitled "Data Review Procedure for Serum Bactericidal Assay Using (b) (4) and (b) (4)," with your response letter. However, you did not provide the document. Please submit document VR-SOP-LC-11208(b) (4) for our review.

Pfizer's Response to Question 4

Pfizer submitted the protocol for processing, reviewing, and reporting (b) (4) as determined by the hSBAs.

Reviewer Comment (KM): The SOP was acceptable.

CBER Question 5

In your response to CBER comment 1c, you state that (b) (4) (b) (4) for each anti-MenACWY hSBA are tested in every assay run, with (b) (4) (b) (4) tested per (b) (4). You further state that as one of the assay criteria, runs are rejected if (b) (4).

of either of the (b) (4) are out of range. While we agree that testing of (b) (4) (b) (4) is important for maintaining consistency of assay performance, it is unclear why you have elected to evaluate the suitability of the (b) (4) calculated from the totality of the samples analyzed per assay run based on (b) (4) that are tested on (b) (4). As (b) (4) variability is expected, it is often customary to assess acceptability of test samples on a (b) (4) basis, where all results from a (b) (4) are deemed invalid if the (b) (4) of the (b) (4) on that (b) (4) are out of specification. Please provide the rationale for your approach and submit data to support the lack of influence of your assessment of control (b) (4) on determination of test samples (b) (4).

Pfizer's Response to Question 5

Pfizer clarified that (b) (4) (b) (4) used to monitor each of the anti-MenB and anti-MenACWY hSBAs are tested on (b) (4) per assay run, such that the (b) (4) determine acceptability of (b) (4) on both a (b) (4) and a per-run basis.

Reviewer Comment (KM): The response is acceptable.

CBER Question 6

In document VR-VTR-10457, you detail the experiments performed with homologous and heterologous antigens to confirm specificity of the anti-MenACWY hSBAs. Although the data you provided provisionally support assay specificity, you only tested potential interference between (a) MenA and MenW and (b) MenC and MenY. Additionally, you only assessed (b) (4) (b) (4) samples for bactericidal titers in each assay, with inhibitory effects of heterologous antigens more often noted when (b) (4) (b) (4) lot was tested vs. the other (e.g., lot (b) (4) in the anti-MenY hSBA). Please submit data to support the lack of inhibition from all of the heterologous MenACWY polysaccharide antigens on each of the hSBAs. Additionally, please provide data from the testing of additional (b) (4) samples (b) (4) to confirm specificity in a greater sample size.

Pfizer's Response to Question 6

Pfizer complied with the request as discussed above under "Updated Specificity Study."

CBER Question 7

In your response to CBER comment 4, you state that clinical samples with (b) (4) higher than the upper limit of quantitation (ULOQ) are (b) (4) (b) (4) prior to generating subsequent (b) (4) (b) (4) with higher (b) (4) (b) (4) utilized if necessary. While we agree in principle with your approach, the suitability of the (b) (4) as a negative (b) (4) is still currently unclear (see comment 2 above). To confirm the lack of an impact of the (b) (4) (b) (4) on determination of (b) (4) at the high end of the assay, please perform parallel testing of (b) (4) samples in both the (b) (4) and an additional (b) (4) such as the (b) (4) described in comment 2 above.

Pfizer's Response to Question 7

Pfizer agreed to conduct the study as requested and submitted data to BLA 125770/0.16 (see "Follow-up to IRs" dated 10 January 2023 and 03 March 2023, below).

CBER Question 8

You state in your responses to CBER comments 3 and 4 that you estimate that you will submit additional data for our review in the first quarter of 2023. Considering evaluation of BLA 125770 will require completion of the additional validation studies previously requested (conveyed on 18 August 2022 in response to IND 17319/110), in addition to those requested in our comments here in response to IND 17319/147, please provide an updated timeline for data submission. Please note that any supportive datasets should be submitted in parallel to IND 17319 and BLA 125770.

Pfizer's Response to Question 8

Pfizer estimated that the appropriate data would be submitted by April 2023. Pfizer submitted the requested data to IND 17319.162 on 31 March 2023, BLA 125300/0.13 on 28 April 2023, and in parallel to BLA 125300/0.16 and IND 17319.270 on 23 May 2023 (see "Updated Validation Studies" and "Updated Specificity Study" above).

Reviewer Comment (KM): *In an attempt to gain insight into the suitability of the (b) (4) and (b) (4) specification margins defined by Pfizer, we sent an IR to the applicant on 03 March 2023:*

03Apr23-IR

[Sent by CBER 03 March 2023. Response received 03April 2023 (STN 125770/0.11)]

CBER Question 1

In your response to CBER comment 3 [submitted to BLA 125770/0.4 on 20 January 2023], you submitted data to support the stability of the anti-MenACWY and anti-MenB human complement serum bactericidal assays (hSBAs) from the time of assay validation through the clinical testing period. For Figures 1–17, you elected to plot titers according to a log2 scale. However, for Figures 18–47, you plotted titers according to a log10 scale, impeding our ability to ascertain the interval of the specification limits for the (b) (4)

(b) (4) We acknowledge the difficulty in plotting the (b) (4) of (b) (4) with multiple specification limits side-by-side in a single graph. Therefore, please submit to BLA 125770 a table defining the specification limits for each of the (b) (4) sera against each of the (b) (4) tested in Figures 18–47.

Pfizer's Response to Question 1

Pfizer provided the tables as requested but clarified that the limits are only used to evaluate long-term trending of assay stability and are not utilized to determine acceptance of test sera in hSBA testing.

Reviewer Comment (KM): Review of the data, in association with discussions with the Statistical Reviewer, indicated that the response is acceptable.

CBER Question 2

In your response to CBER Question 1 [submitted in parallel to IND 17319/158 and BLA 125570/0.7 on 09 February 2023], you describe your rationale for use of (b) (4) in monitoring (b) (4) for the human complement serum bactericidal assays (hSBAs). In your response, you note that (b) (4) are more sensitive to shifts in the assays, and that an (b) (4) margin is appropriate for defining specification limits of the (b) (4). While we agree with your reasoning, it is notable that (b) (4) of the (b) (4) including (b) (4) exhibit specification margins that are (b) (4) when calculated using values equivalent to (b) (4) standard deviations of the mean. While the effects of the (b) (4) specification margins of (b) (4) and (b) (4) are likely minimal due to compensatory co-evaluation of the anti-MenC and anti-MenW hSBAs with the (b) (4) (specification margin = (b) (4)) and (b) (4) (specification margin = (b) (4)) (b) (4) (b) (4) respectively, both the (b) (4) and (b) (4) (b) (4) which you used during clinical sample testing to monitor anti-MenY hSBA performance, exhibit (b) (4) specification margins. Of note, the (b) (4) (b) (4) exhibits a much broader specification margin compared to the (b) (4) that it was introduced to replace, (b) (4) (b) (4) vs. (b) (4), respectively). Considering both of the (b) (4) (b) (4) you currently use to monitor anti-MenY hSBA performance exhibit broad specification margins, we are concerned that the (b) (4) are not suitable for detecting changes in anti-MenY hSBA performance, and that you may have included samples during clinical sample testing that should have been excluded from analyses. Please provide data to demonstrate the impact of narrowing the specification margins for the anti-MenACWY hSBAs to (b) (4) standard deviations of the mean vs. (b) (4) standard deviations of the mean. Please include in your response the percentage of (b) (4) results that would be out of specification, as well as the percentage of clinical test samples that would be out of specification (or would need to be repeated), when applying either specification margin.

Pfizer's Response to Question 2

Pfizer clarified that they did not state in previous responses that an (b) (4) margin would be appropriate for the (b) (4), but rather that use of a (b) (4)(b) (4) to define specification limits would be equivalent to an (b) (4) acceptability margin. The applicant reiterated that the margins as defined were appropriate and in accordance with the GMTs of the (b) (4) each of which was selected in part due to the low relative standard deviation associated with the (b) (4). Pfizer argued that tightening specification limits would result in the unnecessary repeat performance of too many assays without a resultant alteration in reported (b) (4). In

support of this assertion, Pfizer provided data as requested to quantify the number of samples that would have to be re-tested during serological assessment of clinical studies C351001, C351004, and B1971057 should the specification limits have been narrowed.

Reviewer Comment (KM): *Although the number of repeated tests does not form the basis of an acceptable argument for maintaining specification limits as currently defined, the results produced from testing of (b) (4) indicated that all hSBAs appeared to be performing adequately and that no significant assay drift occurred since validation. Therefore, I consider the response acceptable.*

CBER Question 3

In response to CBER Question 6 [submitted in parallel to IND 17319/158 and BLA 125570/0.7 on 09 February 2023], you re-submitted report VR-VTR-10457, entitled “Specificity of Neisseria meningitidis Serogroup ACWY Serum Bactericidal Assay using Human Complement.” In the document, you included tables detailing specificity assays conducted to support performance of the anti-MenACWY hSBAs. However, it is unclear from the data submitted how the average (b) (4) for some of the inhibition experiments, such as those shown in Tables 5–8 of the report, were calculated using the raw data presented in Table 9. For example, you reported a result of (b) (4), respectively, for (b) (4) in the anti-MenA hSBA when (b) (4) antibodies from sample (b) (4) were competitively inhibited with (b) (4) of (b) (4) of (b) (4) (Table 9), which would result in a geometric mean titer of (b) (4) or an arithmetic mean of (b) (4). However, the average (b) (4) reported in the corresponding row of Table 5 is (b) (4). Please provide additional details on the method by which the average (b) (4) were calculated.

Reviewer Comment (KM): *I defer to the Statistical Reviewer to determine acceptability of the response.*

Reviewer Comment (KM): *On 31 March 2023, Pfizer submitted to IND 17319.162 the updated anti-MenB and anti-MenACWY validation reports as requested on 18 August 2022. Prior to their parallel submission to BLA 125770, I reviewed the documents and found that they supported the use of the assays in determination of serological responses to PENBRAYA in clinical studies C1351001, C1351004, and B1971057 (see “Updated Validation Studies” above). However, in the submission to IND 17319.162, Pfizer neglected to submit the accompanying raw data.*

28Apr23-IR

[Sent by CBER 10 April 2023. Response received 28 April 2023 (STN 125770/0.13)]

To support performance of the anti-MenACWY hSBAs in assessment of clinical sample testing, you provided updated validation reports, including documents

VR-MVR-10088, VR-MVR-10091, VR-10092, and VR-MVR-10094, to IND 17319/162. While the data appear to support both precision and linearity in your defined assay ranges, no raw data were provided, impairing our ability to confirm assay suitability. Additionally, for your precision analyses, you evaluated the percentage of results that were within the variation range deemed acceptable for hSBAs with (b) (4) readouts ((b) (4) of the (b) (4)), but did not provide any information regarding the individual coefficient of variation percentages (CV%) attributable to each serum sample. Please provide additional validation data to support suitability of the anti-MenACWY hSBAs, including (a) document VR-MVR-10094-ATT01 containing the raw data from the validation studies and (b) CV% values for each of the individual samples tested in precision analyses. The requested information should be submitted in parallel to IND 17319 and BLA 125770/0.

Please note that the updated validation reports should also be submitted to BLA 125770/0 to facilitate completion of our review of the immunogenicity data from clinical studies B1971057, C3511001, and C3511004.

Pfizer's Response

In addition to the anti-MenACWY hSBA validation reports, Pfizer submitted the individual raw data for each validation study as requested. Pfizer also provided the additional precision analysis as requested.

Reviewer Comment (KM): Data were consistent with the titers documented in the validation reports, confirming suitability of the defined assay ranges. (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4), (b) (4)

(b) (4)

(b) (4)(b) (4). Consistent with the validation reports, the anti-MenA hSBA exhibited

(b) (4)

(b) (4)

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

(b) (4)

The response was

acceptable.

Follow-up to 09Feb23-IR and 03 March 2023

On 23 May 2023, Pfizer submitted in parallel to BLA 125770/0.16 and IND 17319.170 the final datasets requested on 10 January 2023 and 03 March 2023. Data included the results of the updated specificity study and the dilutional study performed on samples >ULOQ.

Reviewer Comment (KM): As discussed in the response to Pfizer's parallel submission to BLA 125770/0.7 and IND 17319.158 (see 09Feb23-IR, above), the results of the specificity study were addressed above under "Updated Stability Study." For the (b) (4) study, Pfizer conducted a small comparability study to demonstrate suitability of (b) (4) samples >ULOQ in the (b) (4) (b) (4) were (b) (4) were compared to those observed when samples were (b) (4) (b) (4) from non-vaccinated donors. For all hSBAs, 100% concordance was observed between samples (b) (4) suggesting comparability of the (b) (4) with (b) (4) Considering the equivalence of the (b) (4) the practice of (b) (4) serum samples >ULOQ with (b) (4) prior to testing in the anti-MenACWY hSBAs is considered acceptable.

Overall Reviewer's Assessment of Relevant Sections of Module 4 and 5:

Pfizer demonstrated that the anti-MenB and anti-MenACWY hSBAs are adequately validated for use in their intended purpose of evaluating serological responses to PENBRAYA in clinical studies C3511001, C3511004, and B1971057. Testing of (b) (4) (b) (4) indicate that assays have remained stable from the time of assay validation through the clinical sample testing period. Specificity studies confirm that the anti-MenACWY hSBAs assays are sufficiently discriminatory (i.e., not susceptible to anti-fHbp antibody-mediated killing) to render additional testing of study participant sera for serogroup-specific IgG responses unnecessary.