

Summary Basis for Regulatory Action

Date:	November 17, 2023
From:	CAPT Mike Smith, PhD, Review Committee Chair
BLA STN:	125770/0
Applicant:	Pfizer Ireland Pharmaceuticals
Submission Receipt Date:	October 21, 2022
Action Due Date:	October 20, 2023
Proper Name:	Meningococcal Groups A, B, C, W, and Y Vaccine
Proprietary Name:	PENBRAYA
Indication:	For active immunization to prevent invasive disease caused by <i>Neisseria meningitidis</i> serogroups A, B, C, W, and Y. PENBRAYA is approved for use in individuals 10 through 25 years of age.

Recommended Action: The Review Committee recommends approval of this product.

Director, Product Office

Discipline Reviews	Reviewer/Consultant, Office/Division
<p>CMC</p> <ul style="list-style-type: none"> • Product • Facilities • Facilities Inspection Waiver Memo Lot Release Protocol and Testing Plan Development • Quality Control (QC), Test Methods, Product Quality 	<p>Lisa Parsons, PhD, OVR/DBPAP James (Erich) Keller, PhD, OVR/DBPAP Lunhua Liu, PhD, OVR/DBPAP Kathryn Matthias, PhD, OVR/DBPAP Jared Greenleaf, PhD, OCBQ/DMPQ Kathleen Jones, PhD, OCBQ/DMPQ Miriam Ngundi, PhD, OCBQ/DMPQ Laura Fontan, PhD, OCBQ/DMPQ Cheryl Hulme, OCBQ/DMPQ</p> <p>Hsiaoling Wang, PhD, OCBQ/DBSQC Tao Pan, PhD, OCBQ/DBSQC Anil Choudhary, PhD, OCBQ/DBSQC Yen Phan, PhD, OCBQ/DBSQC George Kastanis, MS, OCBQ/DBSQC</p>
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<p>Statistical</p> <ul style="list-style-type: none"> • Clinical data • Nonclinical data 	<p>Xinyu Tang, PhD, OBPV/DB Tianjiao Dai, PhD, OBPV/DB</p>
<p>Nonclinical Pharmacology/Toxicology</p> <ul style="list-style-type: none"> • Toxicology • Developmental toxicology 	<p>LCDR Andrew O'Carroll, DVM, MPH OVR/DVRPA</p>
<p>Labeling</p> <ul style="list-style-type: none"> • Promotional Labeling • Proprietary Name Review • Carton and Container Labels • RPM Labeling Review 	<p>Michael Brony, PharmD, OCBQ/APLB CAPT Oluchi Elekwachi, PharmD, MPH, OCBQ/APLB Daphne Stewart, OVR/DVRPA Ching Yim-Banzuelo, OVR/DVRPA Moonsuk Choi, PhD, OVR/DVRPA Maria Bagh, PhD, OVR/DVRPA</p>
<p>Other Reviews</p> <ul style="list-style-type: none"> • CDISC Consult • Clinical Data Analyst Consult • Devices • Regulatory Review 	<p>Brenda Baldwin, PhD, OVR/DVRPA Henry Harry Houghton. PhD, OBPV/DB Andrea Gray, CBER/ORO Brynn Hollingsworth, PhD, OVR/DVRPA Moonsuk Choi, PhD, OVR/DVRPA Maria Bagh, PhD, OVR/DVRPA</p>
<p>Advisory Committee Summary</p>	<p>No Advisory Committee meeting was held.</p>

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1. Introduction

On October 21, 2022, Pfizer Ireland Pharmaceuticals (henceforth referred to as Pfizer or “the Applicant”) submitted a new Biologics License Application (BLA) 125770/0 for a vaccine with the proposed proper name of Meningococcal Groups A, B, C, W, and Y and the proposed proprietary name of PENBRAYA. The indication proposed for PENBRAYA was for active immunization of individuals 10 through 25 years of age to prevent invasive disease caused by *Neisseria meningitidis* serogroups A, B, C, W, and Y.

PENBRAYA is a suspension for injection that is supplied as a sterile Lyophilized MenACWY Component in a vial to be reconstituted with the sterile liquid MenB Component in a pre-filled syringe to form a single dose of vaccine of approximately 0.5 mL. The Lyophilized MenACWY Component of PENBRAYA consists of *N. meningitidis* serogroups A, C, W, and Y polysaccharides individually conjugated to Tetanus Toxoid (TT) carrier protein. The serogroup A, C, W, and Y conjugates are the same conjugates contained in Nimenrix (Pfizer Europe MA EEIG), which is not licensed in the United States (U.S.), but is approved in Europe for use in individuals 6 months of age and older as a single dose or two doses 2 months apart for individuals 6 weeks of age to less than 6 months of age. The MenB Component of PENBRAYA is a sterile suspension composed of two recombinant lipidated factor H binding protein (fHbp) variants from *N. meningitidis* serogroup B, 1 from fHbp subfamily A and 1 from fHbp subfamily B (A05 and B01, respectively), and the two fHbp variants are the same recombinant protein variants contained in Trumenba (Wyeth Pharmaceuticals, Inc). Trumenba is licensed in the U.S. for use in individuals 10 through 25 years of age and can be administered as a 3-dose schedule at 0, 1–2, and 6 months or a 2-dose schedule at 0 and 6 months.

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 infer clinical efficacy. The primary endpoint for evaluating the effectiveness 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. One Phase 3 study was conducted, the pivotal Phase 3 study C3511001, in which immunogenicity of PENBRAYA was compared with 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; supportive studies included B1971057 and C3511004. Additionally, the safety of 2 doses of PENBRAYA was evaluated in comparison with vaccination with U.S.-licensed MenB and MenACWY vaccines in the above three studies and no significant difference was reported.

Based on the above findings, the review committee recommended approval of PENBRAYA for active immunization of individuals 10 through 25 years of age to prevent invasive disease caused by *N. meningitidis* serogroups A, B, C, W, and Y.

2. Background

Invasive Meningococcal Disease

N. meningitidis is a significant cause of endemic and epidemic invasive meningococcal disease worldwide. Six serogroups (A, B, C, W, X and Y) are responsible for the majority of clinical disease, which is commonly meningitis and septicemia. A timely clinical diagnosis is difficult, and, even with available treatments, 10–20% of individuals with meningococcal disease experience

sequelae (e.g., limb loss, neurosensory hearing loss, and seizure disorder) and approximately 10% of cases are fatal.

In 2021, based on Active Bacterial Core (ABC) surveillance data, the Centers for Disease Control and Prevention (CDC) estimated that the overall rate of invasive meningococcal disease was 0.06/100,000 population in the U.S. Rates were 0.02 cases per 100,000 population for adolescents 11 through 17 years of age, and 0.03 cases per 100,000 population for individuals 18 through 22 years of age. Meningococcal disease in the U.S. is often sporadic, but outbreaks of meningococcal disease also occur.

Currently, there are no pentavalent meningococcal conjugate vaccines licensed in the U.S. for active immunization for the prevention of invasive meningococcal disease caused by *N. meningitidis* serogroups A, B, C, W, and Y.

However, there are three quadrivalent meningococcal conjugate vaccines licensed in the U.S. for active immunization for the prevention of invasive meningococcal disease caused by *N. meningitidis* serogroups A, C, W, and Y. Nimenrix, is a quadrivalent meningococcal conjugate vaccine, but it is not licensed in the U.S. (see below).

- GlaxoSmithKline (GSK) manufactures Menveo (Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine) for use in individuals 2 months through 55 years of age; primary immunization is approved for individuals 2 months through 55 years of age, and a single booster dose is approved for individuals 15 through 55 years of age.
- Sanofi manufactures Menactra (Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine) for use in individuals 9 months through 55 years of age; primary immunization is approved for individuals 9 months through 55 years of age, and a single booster dose is approved for use in individuals 15 through 55 years of age.
- Sanofi also manufactures MenQuadfi (Meningococcal (Groups A, C, Y, W) Conjugate Vaccine) for use in individuals 2 years of age and older and should be administered as a single dose. A single booster dose is approved for use in individuals 13 years of age and older who are at continued risk for meningococcal disease if at least 3 years have elapsed since a prior dose of meningococcal (groups A, C, W, Y) conjugate vaccine or a single dose may also be administered if at least 3 years have elapsed since a prior dose of meningococcal polysaccharide vaccine.
- Pfizer manufactures Nimenrix (Meningococcal group A, C, W-135 and Y conjugate vaccine) that is approved for use in Europe in individuals 6 weeks and older. Nimenrix is not licensed for use in the U.S.

Additionally, there are two vaccines licensed in the U.S. for active immunization for the prevention of invasive meningococcal disease caused by *N. meningitidis* serogroup B (see below).

- Pfizer manufactures Trumenba (Meningococcal Group B Vaccine) for use in individuals 10 through 25 years of age and can be administered as a 3-dose schedule at 0, 1–2, and 6 months or a 2-dose schedule at 0 and 6 months. If the second dose is administered earlier than 6 months after the first dose, a third dose should be administered at least 4 months after the second dose.
- GSK manufactures BEXSERO (Meningococcal Group B Vaccine) for use in individuals 10 through 25 years of age and should be administered as a 2-dose schedule at least 1 month apart.

Pfizer manufactured this MenABCWY vaccine to combine the components of their MenACWY and MenB vaccines into one vaccine.

Regarding foreign marketing experience, Trumenba and Nimenrix have both been marketed in Europe, since 2017 and 2012, respectively.

Trumenba Postmarketing Experience

The Applicant has estimated that approximately (b) (4) doses have been distributed worldwide from launch until October 28, 2022.

Cumulatively, as of October 28, 2022, a total of 4246 total postmarketing cases were received and reviewed. The majority of cases (2903, 68.4%) were from the U.S. Of all the reports, 3765 (88.7%) were non-serious, 481 (11.3%) were serious, and one case was fatal. Medical confirmation was obtained in 81.2% of cases. Sex was female in 38%, male in 32.6%, and not reported in 29.3%. Of the total, 2210 (50%) were in the age range of 10 through 25 years, and 1475 (34.7%) did not have an age provided.

The fatality lacked any detailed information on vaccination dates, timing of death, cause of death, concomitant drugs, or patient history to allow for any meaningful assessment.

Nimenrix Postmarketing Experience

The Applicant has estimated that approximately (b) (4) doses have been distributed worldwide from launch until April 19, 2022. Nimenrix is not approved for use in the U.S.

Cumulatively, as of April 19, 2022, a total of 6406 total postmarketing cases were received and reviewed. The cases were from the Netherlands, Italy, United Kingdom, and 53 other countries. Three reports were from the U.S. involving patients who received the vaccine in countries where Nimenrix is approved. Of all the reports, 4810 (75.1%) were non-serious, 1596 (24.9%) were serious, and six cases were fatal. Medical confirmation was obtained in 62.3% of cases. Sex was female in 44.0%, male in 44.9%, and not reported in 11.1%. Of the total, 2356 (36.8%) were in the age range of 10–25 years, and 693 (10.8%) did not have an age provided.

None of the six fatalities occurred in the age range of 10 through 25 years. Four fatalities occurred in infants. Review of the fatalities by the sponsor suggested

alternate causes of death in four of the six reports. One report, in a 49-year-old male, described an acute polyneuropathy developing six days after vaccination and resulting in death. Metronidazole was listed as a concomitant medication but no reason for its use was reported. Another report, in a 12-month-old female, listed an unknown cause of death three days post-vaccination. Though gastroenteritis (GE) was listed, there was no GE reflux, vomiting, diarrhea, appetite changes, or stool changes described in the 2 weeks prior to reporting.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
1. Pre-IND meeting	December 1, 2016
2. IND submission	February 3, 2017
3. Pre-BLA meeting (Written Responses)	Clinical: October 4, 2022 CMC: February 11, 2022
4. BLA 125770/0 submission received	October 21, 2022
5. BLA filed	December 20, 2022
6. Mid-Cycle communication	April 21, 2023
7. Late-Cycle meeting	June 28, 2023
8. Action Due Date	October 20, 2023

3. Chemistry Manufacturing and Controls (CMC)

a. Product Quality

Manufacturing Overview

PENBRAYA is supplied in cartons of 1, 5, and 10 kits, with each kit containing a vial of Lyophilized MenACWY Component, a prefilled syringe containing MenB Component and a 13-mm vial adapter to provide a single dose of PENBRAYA. The liquid MenB Component is used to reconstitute the Lyophilized MenACWY Component to form PENBRAYA immediately prior to administration.

As PENBRAYA is considered a combination product, a CBER device reviewer conducted the review of the pre-filled syringe component. Based on the information provided in the application and cross-referenced master files, as well as additional information submitted subsequently, the device reviewer recommended approval from a device/combination product perspective.

Active ingredients of PENBRAYA consist of four meningococcal capsular polysaccharides (PS) individually conjugated to the carrier protein TT and two lipidated factor H binding protein (fHbp) variants from *N. 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 (b) (4) (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) W and Y (b) (4)

(b) (4) in the 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) (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) (b) (4) site in (b) (4). The MenACWY DP is formulated and filled at the (b) (4) site in (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 where appropriate.

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 (b) (4) stored at (b) (4) in (b) (4) support a shelf life of (b) (4) months. The monovalent (b) (4) conjugates are stored in (b) (4) (b) (4) at (b) (4) with a shelf life of (b) (4). The MenB fHbp proteins are stored in (b) (4) at (b) (4) with a shelf life of (b) (4) months. 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.

Drug Substance (DS)

Pfizer listed the following (b) (4) in section 3.2.S entitled, “3.2.S (b) (4) (b) (4)” for STN 125770/0: MnB (b) (4) subfamily A, MnB (b) (4) subfamily B, (b) (4) (b) (4)

Drug Product (DP)

Pfizer listed the following three DPs in section 3.2.P entitled, “3.2.P Drug Product” for STN 125770/0: MnB Bivalent (b) (4) MenACWY-TT and MenABCWY. Although Pfizer refers to MnB Bivalent (b) (4) and MenACWY-TT as DPs, CBER considers them to be DP Components and the final DP to be MenABCWY.

Composition

Each approximately 0.5 mL dose of PENBRAYA contains *N. meningitidis* serogroup A, C, W, and Y polysaccharide (5 mcg each; 20 mcg total) conjugated to tetanus toxoid (44 mcg tetanus toxoid), 2 recombinant lipidated factor H binding protein variants from *N. meningitidis* serogroup B (60 mcg each; total of 120 mcg protein), L-histidine (0.78 mg), trometamol (0.097 mg), sucrose (28 mg), aluminum phosphate (0.25 mg aluminum), sodium chloride (4.65 mg), and PS80 80 (0.018 mg) at pH 6.0.

PENBRAYA does not contain any preservatives.

Dating Period

The dating period for the Lyophilized MenACWY Component of Meningococcal Groups A, B, C, W, and Y Vaccine shall be 18 months from the date of manufacture when stored at 2–8°C. The dating period for the MenB Component of Meningococcal Groups A, B, C, W, and Y Vaccine shall be 24 months from the date of manufacture when stored at 2–8°C. The dates of manufacture for the Lyophilized MenACWY Component and the MenB Component shall be defined as the dates when filling into final containers is initiated. Following the final sterile filtration, no reprocessing/reworking is allowed without prior approval from the Agency. The expiration date for the packaged product, Lyophilized MenACWY Component plus MenB Component, shall be dependent on the shortest expiration date of any component.

Product-related assays

Pfizer submitted validation study results for (b) (4) for MenACWY-TT and MenABCWY and (b) (4) potency and (b) (4) for MenB Component. The validation of the MenB Component assays was acceptable, but the validation of nephelometry did not adequately demonstrate that Pfizer’s routine testing lab has acceptable accuracy, precision, and linearity over the assay’s range because Pfizer neither assessed all validation parameters at their routine testing lab nor assessed all validation parameters at their original testing lab and demonstrated equivalence between the original and routine lab. CBER requested supplemental analyses to remedy these issues. While Pfizer’s response did not fully address CBER’s concerns, CBER performed additional analyses and concluded that the validation of (b) (4) did demonstrate acceptable performance. The routine testing lab is considered acceptably validated for this (b) (4)

MenACWY-TT was previously marketed by another manufacturer in the European Union as Nimenrix and was acquired by Pfizer in 2015. Pfizer conducted transfer studies to demonstrate the equivalence from the previous manufacturer and Pfizer's labs when performing the (b) (4) (b) (4) assays. While Pfizer did not fully address CBER's concerns about their statistical methods not accounting for correlation induced by the transfer study design, the totality of evidence suggest that Pfizer has acceptable assay performance for these assays. Pfizer also established equivalence of the interim, primary, and working reference materials for MenACWY-TT and MenABCWY.

Overall, the statistical issues in the CMC validation studies and analyses were resolved during the BLA review, and Pfizer's labs have acceptable performance for the critical DP assays.

Comparability Protocols (CPs)

Pfizer submitted CPs for the following:

- 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)
- (b) (4)

- (b) (4)

b. Testing Specifications

The analytical methods and their validations and/or qualifications reviewed for the PENBRAYA drug substances and drug product were found to be adequate for their intended use.

c. CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of PENBRAYA are listed in Table 2 below. The activities performed and inspectional

histories are noted in the table and are further described in the paragraphs that follow.

Table 2. Manufacturing Facilities for Meningococcal Groups A, B, C, W and Y Vaccine (PENBRAYA)

Name/Address	FEI number	DUNS number	Inspection/ Waiver	Justification/ Results
(b) (4) <i>Drug substance manufacturing</i>	(b) (4)	(b) (4)	Waiver	(b) (3) (A), (b) (4) CDER/OPQ PAI (b) (4) VAI
Pfizer Ireland Pharmaceuticals (b) (4) (b) (4) <i>Drug substance manufacturing, drug product manufacturing, and final release testing</i>	(b) (4)	(b) (4)	Waiver	ORA/OBPO (b) (4) NAI
(b) (4) <i>Drug substance intermediate manufacturing</i>	(b) (4)	(b) (4)	Waiver	(b) (3) (A), (b) (4) Compliant ORA/OBPO (b) (4) VAI
(b) (4) <i>Drug product manufacturing and final release testing</i>	(b) (4)	(b) (4)	Waiver	ORA/OBPO (b) (4) NAI

CDER – Center for Drug Evaluation and Research; (b) (3) (A), (b) (4)
 (b) (3) (A), (b) (4) NAI – No Action Indicated; OBPO – Office of Biological Products Operations; OPQ – Office of Pharmaceutical Quality; ORA – Office of Regulatory Affairs; PAI – pre-approval inspection; VAI – Voluntary Action Indicated

An inspection of (b) (4) was performed by (b) (3) (A), (b) (4) . CDER/OPQ conducted a PAI of the facility from (b) (4) All inspectional issues were resolved, and the inspection was classified as VAI.

A surveillance inspection of Pfizer Ireland Pharmaceuticals was conducted by OBPO from (b) (4) No Form FDA 483 was issued, and the inspection was classified as NAI.

An inspection of (b) (4) was performed by (b) (3) (A), (b) (4) OBPO conducted a surveillance inspection of the facility from (b) (4) All inspectional issues were resolved, and the inspection was classified as VAI.

A surveillance inspection of (b) (4) was conducted by OBPO from (b) (4) No Form FDA 483 was issued, and the inspection was classified as NAI.

e. Container/Closure System

MenABCWY Vaccine DP

The MenABCWY DP is a co-packaged combination product that consists of the following components: one single-dose vial of the lyophilized MenACWY-TT DP, one prefilled syringe containing the MnB Bivalent (b) (4) DP component, and one sterile 13 mm polycarbonate vial adapter.

The MenACWY-TT DP is filled into 2 mL Type (b) (4) clear borosilicate glass vials that are manufactured by (b) (4) or (b) (4) (b) (4) The vial is closed with a 13 mm siliconized bromobutyl-rubber lyophilization stopper and an aluminum seal with a tamper-evident polypropylene flip-off cap. The stopper is manufactured by (b) (4) (b) (4) and the crimp seal is manufactured by (b) (4) (b) (4) (b) (4) performed the container closure integrity testing (CCIT) employing the (b) (4) test method; all acceptance criteria were met.

The MnB Bivalent (b) (4) DP is filled into 1 mL Type (b) (4) borosilicate glass syringes with the barrel (b) (4) (b) (4) The syringes are manufactured by (b) (4) (b) (4) The (b) (4) syringes are pre-assembled with a (b) (4) (b) (4) and the (b) (4) syringes are pre-assembled with a (b) (4) (b) (4) Both tip cap assemblies include a non-product contact

polycarbonate Luer lock adapter, a non-product contact polypropylene rigid cap, and a product contact elastomeric tip cap. The tip cap elastomer is a (b) (4) latex-free, gray synthetic isoprene/bromobutyl blend rubber and is manufactured by (b) (4) (b) (4). The closure for the syringe is a plunger stopper composed of (b) (4) latex-free gray chlorobutyl rubber, manufactured by (b) (4) (b) (4). The plunger stopper is also (b) (4) (b) (4). A non-product contact polypropylene plunger rod and a non-product contact polypropylene finger grip (backstop) are also included. Pfizer Ireland Pharmaceuticals performed the CCIT employing the (b) (4) test method; all acceptance criteria were met.

The vial adapter is designed to connect the prefilled syringe of the MnB Bivalent (b) (4) DP (via Luer lock connection) to the vial of the MenACWY-TT DP (via puncture spike assembly) for reconstitution. The vial adapter is individually packaged, 510(k) cleared, and supplied by (b) (4) or (b) (4) (b) (4).

f. Environmental Assessment

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.

4. Nonclinical Pharmacology/Toxicology

This application does not contain any nonclinical toxicology studies for PENBRAYA. Rather, the nonclinical toxicology program consists of the studies for the for two components of the vaccine, Trumenba and Nimenrix, MenB Component and Lyophilized MenACWY Component, respectively. Trumenba is licensed in the U.S. and this application includes both repeat-dose toxicity and developmental and reproductive toxicity (DART) studies used for the original U.S. licensure. Nimenrix is currently licensed in 79 countries globally and a package of repeat-dose toxicity, DART and local tolerance studies are included in this application. Additionally, there are a series of five mixed toxicity studies conducted to provide nonclinical safety and risk assessment for (b) (4) (b) (4) the activated polysaccharides in the vaccine.

There are no toxicologic issues identified which would preclude approval of this application in the intended human population. Treatment-related effects were limited to those which are considered anticipated sequelae of the intended immune response to vaccination and there were no effects on embryonic or postnatal development following maternal vaccination.

5. Clinical Pharmacology

Mechanism of Action

Protection against invasive meningococcal disease is conferred mainly by complement-mediated antibody dependent killing of *N. meningitidis*.¹ Vaccination with PENBRAYA induces the production of bactericidal antibodies specific to the capsular polysaccharides of *N. meningitidis* serogroups A, C, W, and Y and to fHbp subfamily A and B variants of *N. meningitidis* group B. The susceptibility of group B meningococci to bactericidal antibody is dependent upon both the antigenic similarity of the fHbp subfamily A or subfamily B vaccine antigen to the fHbp protein expressed by the bacterial strain and the amount of fHbp expressed at the bacterial surface.²

6. Clinical/Statistical

a. Clinical Program

The Applicant included data from three clinical studies that were all conducted under IND 17319 and the design of the studies were agreed upon with CBER prior to submission of the BLA. The BLA was approved under the traditional pathway. The clinical studies that will be discussed in this SBRA are shown below in Table 3.

Table 3. Overview of Clinical Studies

Study Number / Location / Participant Age	Description	Vaccination Schedule	Safety Population MenABCWY	Safety Population MenB + MenACWY-CRM
Vaccination (0- and 6-Month Schedule)	--	--	--	--
C3511001 USA, Europe 10–25 years of age	Phase 3, randomized, active-controlled, observer-blind, safety and immunogenicity	<u>MenABCWY</u> Month 0: MenABCWY + saline Month 6: MenABCWY <u>Comparator</u> Month 0: MenB + MenACWY-CRM Month 6: MenB	1763	649
B1971057 Stage 1 USA, Europe 10–25 years of age	(First-in-human study for MenABCWY) randomized, active-controlled, observer-blind, safety and immunogenicity	<u>MenABCWY</u> Month 0: MenABCWY + saline Month 6: MenABCWY <u>Comparator</u> Month 0: MenB + MenACWY-CRM Month 6: MenB	543	1057
Extended Interval (0- and 12-Month Schedule)	--	--	--	--
C3511004 USA 11–14 years of age	Phase 2, randomized, observer-blind [only safety and immunogenicity data through Month 13 were included in the BLA] ^a	<u>Group 1: MenABCWY 0- and 12-month schedule</u> Month 0: MenABCWY Month 12: MenABCWY <u>Group 2: MenABCWY 0- and 36-month schedule</u> Month 0: MenABCWY Month 12: Saline Month 36: MenABCWY	<u>Group 1</u> N=146 <u>Group 2</u> N=148	0
Booster Vaccination	--	--	--	--

Study Number / Location / Participant Age	Description	Vaccination Schedule	Safety Population MenABCWY	Safety Population MenB + MenACWY-CRM
B1971057 Stage 2 USA, Europe 14–30 years of age	Phase 2, randomized, active-controlled, open-label Booster Vaccination 4 years after Vaccination 2	MenABCWY Booster Vaccination 4 years after MenABCWY Vaccination 2 MenB + MenACWY-CRM Booster Vaccination 4 years after Trumenba Vaccination 2	144	96
Total	--	--	2744	1802

Source: Adapted from clinical-overview.pdf, Table 1.

Abbreviations: BLA=Biologics License Application; MenABCWY=Neisseria meningitidis groups A, B, C, W, and Y vaccine; MenB=meningococcal serogroup B factor H binding protein (Trumenba); MenACWY-CRM=meningococcal (serogroups A, C, W and Y) oligosaccharide diphtheria CRM197 conjugate vaccine (Menveo)

Immunogenicity (Effectiveness)

Protection against invasive meningococcal disease is conferred mainly by complement-mediated antibody-dependent killing by bactericidal antibodies specific to the capsular polysaccharides of *N. meningitidis* serogroups A, C, W, and Y and to fHbp present in the outer membrane of *N. meningitidis* group B. Effectiveness was evaluated by measuring antibodies with assays that uses human complement to assess serum bactericidal activity (hSBA). MenABCWY effectiveness was demonstrated by showing that hSBA responses to serogroups A, B, C, W and Y following the combination vaccine were non-inferior to hSBA responses one month following the last vaccination with U.S.-licensed MenB and MenACWY vaccines. The susceptibility of group B meningococci to bactericidal antibody is dependent upon both the antigenic similarity of the fHbp subfamily A or subfamily B vaccine antigen to the fHbp protein expressed by the bacterial strain and the amount of fHbp expressed at the bacterial surface. The four primary MenB strains each expressed a variant from subfamily A or B (i.e., A22, A56, B24, B44), including test strains expressing prevalent fHBP variants in the U.S. (B24 and A22). The primary strains expressing low or medium quantities of fHBP were chosen to ensure a stringent measure of anti-fHBP-mediated bactericidal killing.

Study C3511001 was designed as a randomized, active-controlled, observer-blinded study conducted in individuals 10 through 25 years of age in the U.S. and Europe. MenABCWY (N=1763) or meningococcal group B vaccine (Trumenba; MenB) (N=650) was administered at 0 and 6 months. Meningococcal groups A, C, Y, and W oligosaccharide diphtheria CRM₁₉₇ conjugate vaccine (MenACWY-CRM, GSK Vaccines, SRL) was concomitantly administered with Trumenba at Month 0. All participants were MenB vaccine naïve. MenACWY conjugate vaccine-naïve and MenACWY conjugate vaccine-experienced participants were enrolled in the study. The primary endpoints for seroreponses to Men A, C, W, Y components (ACWY vaccine-naïve and ACWY vaccine-experienced participants) and the B components (seroresponse using 4 MenB primary strains, composite response) were met.

Seroresponse was defined as a ≥ 4 -fold increase in hSBA post-vaccination titer compared to pre-vaccination titer. Composite response was defined as the percentage of participants with post-vaccination hSBA titer greater than the LLOQ for all 4 primary MenB strains.

For MenACWY seroresponse, the noninferiority (NI) criteria following MenABCWY Dose 2 compared to a single dose of MenACWY-CRM were met: the lower limit (LL) of the 95% confidence interval (CI) for the percentage difference in participants with a seroresponse to each serogroup was $> -10\%$ (ACWY vaccine-naïve participants: LL was -0.2, 34.4, 18.8, and 18.0, respectively, for MenA, C, W, and Y; ACWY vaccine-experienced participants: in the same order, the LL was -6.5, -4.6, -2.2, and -4.6, respectively). See Table 4 below.

Table 4. Seroreponse Rate Percentages (A,C,W,Y) at 1 Month After MenABCWY Dose 2 Versus 1 Month After MenACWY CRM Dose 1, Evaluable Immunogenicity Population, Study C3511001

Serogroup ACWY Vaccination History	MenABCWY Dose 2 ^a Seroreponse Rate % ^c N=439-451 (Naïve) N=376-387 (Experienced)	MenACWY-CRM Dose 1 ^b Seroreponse Rate % ^c N=244-254 (Naïve) N=222-227 (Experienced)	Difference in Seroreponse Rate (MenABCWY – MenACWY-CRM) % (95%CI) ^d
A	--	--	--
ACWY-naïve	97.8	95.3	2.5 (-0.2, 6.0)
ACWY-experienced	93.8	96.9	-3.2 (-6.5, 0.5)
C	--	--	--
ACWY-naïve	93.3	52.4	41.0 (34.4, 47.5)
ACWY-experienced	93.8	94.7	-0.9 (-4.6, 3.3)
W	--	--	--
ACWY-naïve	97.3	73.0	24.3 (18.8, 30.4)
ACWY-experienced	97.1	96.4	0.7 (-2.2, 4.3)
Y	--	--	--
ACWY-naïve	94.4	70.6	23.8 (18.0, 30.1)
ACWY-experienced	93.0	93.7	-0.7 (-4.6, 3.8)

Source: Adapted from c3511001-report-body.pdf, Table 13.

Abbreviations: CI=confidence interval; hSBA=serum bactericidal assay using human complement; LL=lower limit; LLOQ=lower limit of quantitation; LOD=limit of detection; MenACWY-CRM=meningococcal (serogroups A, C, W and Y) oligosaccharide diphtheria CRM197 conjugate vaccine (Menveo); MenB=meningococcal serogroup B factor H binding protein (Trumenba).

a. MenABCWY + saline administered at 0 month followed by MenABCWY at 6 months.

b. MenB and MenACWY-CRM administered at 0 month followed by MenB at 6 months.

c. %=n/N. n=number of participants with hSBA titer fold rise ≥ 4 from baseline (pre-Dose 1) for the given strain. N=number of participants with valid and determinate hSBA titers for the specified strain at both the given sampling time point and baseline. Seroreponse was defined as ≥ 4 -fold increase, as follows: (1) For participants with a baseline hSBA titer $< 1:4$ (LOD), a ≥ 4 -fold response was defined as an hSBA titer $\geq 1:16$. (2) For participants with a baseline hSBA titer $\geq \text{LOD}$ and $< \text{LLOQ}$, a ≥ 4 -fold response was defined as an hSBA titer ≥ 4 times the LLOQ. (3) For participants with a baseline hSBA titer $\geq \text{LLOQ}$, a ≥ 4 -fold response was defined as an hSBA titer ≥ 4 times the baseline titer. The LLOQ=1:8 for serogroups A, C, W, and Y.

d. Noninferiority was demonstrated if LL of the 2-sided 95% CI for the percentage difference in participants with a seroreponse for Men A, C, W, and Y was $> -10\%$.

For MenB responses, the NI criteria following MenABCWY Dose 2 compared to MenB Dose 2 were met for the 5 endpoints (4 MenB primary strains, composite endpoint); the LL of the 2-sided 95% CI for the percentage difference of participants with seroreponse using each primary MenB test strain and for the percentage difference of participants with a composite response was $> -10\%$; for the primary MenB test strain expressing A22, A56, B24, or B44 variant, the LL was -0.7, -1.0, 5.2, and 2.9, respectively, and 4.2 for the composite response. See Table 5 below.

Table 5. Serogroup B Seroreponse Rate Percentages and Composite Response at 1 Month After MenABCWY Dose 2 Versus MenB Dose 2, Evaluable Immunogenicity Population, Study C3511001

Serogroup B Variant	MenABCWY Dose 2 ^a Seroreponse Rate % ^c N=755–845	MenB Dose 2 ^b Seroreponse Rate % ^c N=383–419	Difference in Seroreponse Rate (MenABCWY – MenACWY-CRM) % (95% CI) ^d
Seroreponse ^e	--	--	--
A22	83.0	79.0	4.0 (-0.7, 8.9)
A56	95.9	94.5	1.4 (-1.0, 4.3)
B24	68.1	57.2	10.9 (5.2, 16.6)
B44	86.5	79.2	7.3 (2.9, 11.9)
Composite ^e	--	--	--
Pre-Dose 1	1.2	2.0	
Post-Dose 2	78.3	68.7	9.6 (4.2, 15.2)

Source: Adapted from c3511001-report-body.pdf, Table 14.

hSBA assay using primary MenB strains PMB80 (variant A22), PMB2001 (variant A56), PMB2948 (B24), PMB2707 (B44).

a. MenABCWY + saline administered at 0 month followed by MenABCWY at 6 months.

b. MenB and MenACWY-CRM administered at 0 month followed by MenB at 6 months.

c. % = n/N. n = number of participants with hSBA titer fold rise ≥ 4 from baseline (pre-Dose 1) for the given strain. N = number of participants with valid and determinate hSBA titers for the specified strain at both the given sampling time point and baseline. Seroreponse was defined as ≥ 4 -fold increase, as follows: (1) For participants with a baseline hSBA titer $< 1:4$ (LOD), a ≥ 4 -fold response was defined as an hSBA titer $\geq 1:16$. (2) For participants with a baseline hSBA titer \geq LOD and $<$ LLOQ, a ≥ 4 -fold response was defined as an hSBA titer ≥ 4 times the LLOQ. (3) For participants with a baseline hSBA titer \geq LLOQ, a ≥ 4 -fold response was defined as an hSBA titer ≥ 4 times the baseline titer. The LLOQ = 1:16 for A22; 1:8 for A56, B24, and B44.

d. Noninferiority was demonstrated if LL of the 2-sided 95% CI for the percentage difference in participants with a seroreponse for serogroup B (4 primary strains, composite response) was $> -10\%$.

e. Composite response was defined as an hSBA titer \geq LLOQ for all 4 primary MenB strains.

Since noninferiority was demonstrated for MenABCWY primary MenB responses compared with Trumenba for the primary endpoints and MenB responses were comparable for secondary outcomes (GMT, percentage of participants with hSBA titer greater than the assay LLOQ, reverse cumulative distribution curves [RCDCs]), as observed in Study B1971057, MenABCWY secondary Men B strain evaluation was not performed.

Among ACWY vaccine-experienced participants, the MenA and Men C hSBA GMT after 2 doses of MenABCWY was lower than GMTs to both serogroups after 1 dose of MenACWY-CRM. However, the differences in hSBA GMTs were not reflected in lower seroreponse rates. In the limited antibody persistence data from Study B1971057 Stage 2, similar proportions of participants who received two doses of MenABCWY maintained hSBA titers \geq LLOQ for all four serogroups compared with those who received MenACWY-CRM + MenB. Therefore, in the population studied, the observed hSBA GMT differences between groups are unlikely to result in lower rates of protection over time.

Key immunogenicity results from all of the studies are summarized as follows:

- For the MenACWY noninferiority (NI) evaluation in ACWY-naïve participants, percentage of subjects achieving seroreponse ranged from 93.3% to 97.8% after 2 doses of MenABCWY and ranged from 52.4% to 95.3% after 1 dose of MenACWY-CRM for the ACWY test strains. The differences in percentages (2 doses of MenABCWY versus 1 dose of MenACWY-CRM) ranged from 2.5% to 41.0% across ACWY strains. The lower limits (LLs) of the 2-sided 95%

confidence intervals (CIs) for the differences in percentages are greater than -10% for all ACWY strains, meeting the NI criteria for 2 doses of MenABCWY compared with 1 dose of MenACWY-CRM in ACWY-naïve participants.

- For the MenACWY NI evaluation in ACWY-experienced participants, percentages of subjects achieving seroresponse ranged from 93.0% to 97.1% after 2 doses of MenABCWY and ranged from 93.7% to 96.9% after 1 dose of MenACWY-CRM. The differences in percentages (2 doses of MenABCWY versus 1 dose of MenACWY-CRM) ranged from -3.2% to 0.7% across ACWY strains. The LLs of the 2-sided 95% CIs for the differences in percentages are greater than -10% for all ACWY strains, meeting the NI criteria for 2 doses of MenABCWY compared with 1 dose of MenACWY-CRM in ACWY-experienced participants.
- For the MenB NI evaluation, percentages of subjects achieving seroresponse ranged from 68.1% to 95.9% after 2 doses of MenABCWY and ranged from 57.2% to 94.5% after 2 doses of Trumenba for the four primary MenB strains. The differences in percentages (2 doses of MenABCWY versus 2 doses of Trumenba) ranged from 1.4% to 10.9% across primary MenB strains. Additionally, percentages of subjects achieving composite response were 78.3% and 68.7% after 2 doses of MenABCWY and Trumenba, respectively, resulting in a difference of 9.6%. The LLs of the 2-sided 95% CIs for the differences in percentages (2 doses of MenABCWY versus 2 doses of Trumenba) are greater than -10% for all 4 primary MenB strains and the composite endpoint, meeting the NI criteria for 2 doses of MenABCWY compared with 2 doses of Trumenba.

Clinical serological assays

The validation reports of the hSBAs against *N. meningitidis* serogroup B strains were reviewed during the approval of STN 125549 for Trumenba®. The validation reports of the hSBAs against *N. meningitidis* serogroup A (MenA) strain (b) (4) serogroup C (MenC) strain (b) (4) serogroup W (MenW) strain (b) (4) and serogroup Y (MenY) strain (b) (4) were reviewed for this Application and they were submitted in Module 5.3.1.4 of STN 125770/0.0 and STN 125770/0.13. The specificity reports of these assays were submitted in Module 5.3.1.4 of STN 125770/0.7 and STN 125770/0.16. 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)

respectively.

The validation results demonstrated acceptable accuracy and precision in the assay ranges for each of the anti-MenACWY hSBAs. The lower and upper limits of quantitation (LLOQ and ULOQ) were determined to be (b) (4) and (b) (4) for anti-MenA and anti-MenC hSBAs and (b) (4) and (b) (4) for anti-MenW and anti-MenY hSBAs. The limit of detection (LOD) was determined to be (b) (4) for all anti-ACWY hSBAs.

The specificity results showed that for each of the anti-MenACWY hSBAs, competition with heterologous MenACWY polysaccharides, irrelevant meningococcal B proteins ((b) (4) A and (b) (4) B), and irrelevant pneumococcal polysaccharides resulted in minor hSBA titer (b) (4). When competed with homologous polysaccharides, all (b) (4) serum samples tested per serogroup showed a (b) (4) in titer at (b) (4) or more competitor concentrations, except for MenC, where (b) (4) out of (b) (4) serum samples tested showed a (b) (4) in titer at (b) (4) or more competitor concentrations. Some serum samples may have residual bactericidal antibodies at the lower concentrations that may still be sufficient to induce killing; thus, it is not uncommon to observe one or two samples that are not inhibited in the presence of even the highest concentration of homologous antigen. As such, the specificity results are acceptable for the anti-MenACWY hSBAs. Overall, the hSBAs used in the evaluation of clinical endpoints for the Phase 3 study were adequate for their intended uses.

Overall, review of the clinical trial design, the pre-specified endpoints and statistical success criteria, and immunogenicity results support the effectiveness of MenABCWY administered at 0 and 6 months to individuals 10 through 25 years of age.

Safety

The safety of MenABCWY in individuals 10 through 25 years of age was evaluated in 3 studies (2744 MenABCWY, 1802 comparator). In the two active controlled studies (C3511001, B1971057 Stage 1), 2306 participants received at least 1 dose of MenABCWY and 1706 received a comparator vaccine(s) [vaccination Visit 1: MenB+MenACWY-CRM; vaccination Visit 2: MenB]. A total of 1792 participants (vaccine and comparator groups combined) had a history of prior meningococcal conjugate vaccination. Study B1971057 Stage 2 included 144 MenABCWY and 96 comparator participants. In Study C3511004, a total of 294 participants received MenABCWY.

The safety monitoring for Study C3511001 and B1971057 Stage 1 were the same; solicited local and systemic adverse reactions were monitored for 7 days after study vaccination using an electronic diary (e-diary). Spontaneous reports of adverse events (AEs) were collected through 1 month after the last vaccination, and through 6 months after the last vaccination for serious adverse events (SAEs) and newly diagnosed chronic medical conditions (NDCMCs). In Study C3511001, the most commonly reported ($\geq 15\%$) solicited adverse reactions after Dose 1 and Dose 2, respectively, were pain at the injection site (89% and 84%), fatigue (52% and 48%), headache (47% and 40%), muscle pain (26% and 23%), injection site redness (26% and 23%), injection site swelling (25% and 24%), joint pain (20.2% and 18.3%), and chills (20.1% and 16.4%).

In the 2 controlled studies (C3611001, B1971057 Stage 1), the most common non-serious unsolicited AEs reported within 30 days after any vaccination were events in the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) of *Infections and Infestations* and *Injury, Poisoning and Procedural Complications*; the events were anticipated for a study population of adolescents

and young adults. During the time period from the first study visit through 6 months after the last vaccination, SAEs were reported by 0.9% of participants in the MenABCWY group and 1.1 % of participants in the comparator group, and most commonly reported in the SOCs of *Injury, Poisoning and Procedural Complications* and *Psychiatric Disorders*. Upon review of the case narratives, none of the SAEs were assessed by FDA/CBER clinical review team to be related to MenABCWY.

Overall (3 studies), an autoimmune condition with confirmed diagnosis was reported for 0 MenABCWY and 7 (0.4%) MenB+MenACWY-CRM participants, a neuroinflammatory condition with confirmed diagnosis was reported for 2 (0.07%) MenABCWY participants and 1 (0.06%) MenB+MenACWY-CRM participant. Upon review of the case narratives, none of the autoimmune or neuroinflammatory conditions were assessed by FDA/CBER clinical review team to be related to MenABCWY.

The Core Safety Dataset includes data from Studies C3511001 and B1971057 Stage 1. The overall safety dataset includes, in addition, participants from the Extended Interval Study C3511004. Results of safety data from participants of study B1971057 Stage 2 is not integrated but reported separately.

Demographic Information: Subgroup Demographics and Analysis Summary

Overall, for serogroups A,C,W,Y and MenB expressing the A22 variant, the seroresponse rates (defined as the percentage of participants with ≥ 4 -fold increase in one month post-vaccination hSBA titer compared with pre-vaccination 1) in participants 18 through 25 years of age (hereafter abbreviated 18-25 years of age) was lower than seroresponse rates in participants 10 through <18 years of age (hereafter abbreviated 10-<18 years of age), due to higher baseline titers prior to Vaccination 1. hSBA responses among females and males were similar.

In Study C3511001, the percentage of MenABCWY participants reporting any solicited systemic reaction after any vaccination was notably higher in females (F) (87.2%) compared to males (M) (75.6%), mainly due to differences in headache (F 65.6%, M 49.2%) and fatigue (F 69.8%, M 57.5%). There were no clinically important differences in the percentage of MenABCWY participants who reported any solicited local reactions after any vaccination in subgroup analyses by sex or solicited reactions (local or systemic) by age (10 to <18 years of age, 18 to <26 years of age).

No definitive conclusions could be made about differences in hSBA responses or frequencies of solicited reactions by race, ethnicity, or geographic region, since >74% of participants of the overall study population were White or non-Hispanic/non-Latino.

Overall Conclusions from Clinical Studies

The safety and immunogenicity data submitted in this BLA support the use of MenABCWY, administered as a 2-dose series (at 0 and 6 months) for active immunization to prevent invasive disease caused by *N. meningitidis* serogroups A, B, C, W, and Y in individuals 10 through 25 years of age.

b. Bioresearch Monitoring (BIMO)–Clinical/Statistical/Pharmacovigilance

Bioresearch Monitoring (BIMO) Clinical Investigator (CI) inspection assignments were issued for four clinical study sites that participated in the conduct of protocol C3511001. The inspections did not reveal substantive issues that impact the data submitted in this Biologics License Application (BLA).

c. Pediatrics

The Applicant's Pediatric Plan was presented to Pediatric Review Committee (PeRC) on August 15, 2023. The committee agreed with the Applicant's request for a waiver from birth to <1 year of age because there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in that age group (section 505B(a)(5)(B)(ii) of PREA). The committee also agreed with the Applicant's request for a partial deferral from 1 to <10 years of age because the biological product is ready for approval for use in adults before pediatric studies are complete (section 505B(a)(4)(A)(i)(I) of PREA).

The PREA-required studies specified in the approval letter and agreed upon with the Applicant are as follows:

1. Study B1971067 to evaluate the safety and immunogenicity of MenABCWY in individuals 1 to <10 years of age
2. Study C3511005 to evaluate the safety and immunogenicity of MenABCWY ages 1 to <10 years of age

The Applicant has fulfilled the pediatric study requirements for ages 10 to <18 years for this application.

d. Other Special Populations

N/A

7. Safety and Pharmacovigilance

Table 6. Pfizer's Pharmacovigilance Plan

Type of Concern	Safety Concern	Proposed Action
Identified	None	Not applicable
Potential	None	Not applicable
Missing	Exposure during pregnancy and lactation	Summary and analysis of all reports of exposure during pregnancy and lactation in the post-marketing dataset in each periodic safety report for both interval and cumulative data. Pregnancy registry study

Adapted from Table 2 and 3, U.S. Risk Management Pharmacovigilance Plan Version 1.2 770/0.21, Module 1.16

The Sponsor proposes the following pregnancy registry study as a Postmarketing Commitment (PMC).

Title: A Pregnancy Registry Study to Evaluate the Safety of PENBRAYA Meningococcal Vaccine Exposure During Pregnancy

Study Objective:

To assess spontaneous abortion, stillbirth, preterm birth, small for gestational age, and major congenital malformation among pregnant individuals exposed to PENBRAYA any time during pregnancy or within 30 days prior to last menstrual period (LMP).

Study Design:

Non-intervention prospective cohort pregnancy registry in the US. Enrolled participants will be followed through the end of pregnancy and all liveborn infants will be followed through 6 months of age.

Study Participants:

Pregnant individuals who receive at least one dose of PENBRAYA any time during pregnancy or within 30 days prior to LMP.

Study Duration:

Enrollment will occur for six years with sufficient time (up to two years) after enrollment to account for the follow-up to be complete for the last enrolled participant.

8. Labeling

The proposed proprietary name, PENBRAYA, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on January 9, 2023, and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on January 18, 2023.

The Advertising and Promotional Labeling Branch (APLB) reviewed the proposed Prescribing Information and Package and Container Labels on June 16, 2023, and found them acceptable from a promotional and comprehension perspective.

All labeling issues regarding the PI and the carton and container labels were acceptably resolved after exchange of information and discussions with the Applicant.

In the prescribing information for MenABCWY the Applicant proposed to include statements in the Dosage and Administration section of the prescribing information indicating that:

1. A (b) (4) of MenABCWY provides protection against disease caused by serogroups A, C, W, and Y.
2. (b) (4)

3. The interval between the first and second dose of the 2-dose series can be 6 (b) (4) months.

Statements indicating that a (b) (4) of MenABCWY prevents disease caused by serogroups A, C, W and Y, either as an initial immunization or as the second dose of MenACWY in individuals who have previously received their first MenACWY conjugate vaccine, were not included in the prescribing information for the following reasons:

- The Dosage and Administration section of labeling provides the information needed for safe and effective use of MenABCWY to prevent invasive disease caused by *N. meningitidis* serogroups A, B, C, Y and W. Inclusion of a sentence in Dosage and Administration that (b) (4) of MenABCWY provides protection against serogroups A, C, W and Y implies that a (b) (4) (b) (4) of MenABCWY is an approved dosing regimen and is not consistent with the requirement for a two-dose schedule to provide protection against *N. meningitidis* serogroups A, B, C, W and Y.
- A (b) (4) of MenABCWY should not be administered when protection from invasive disease caused by *N. meningitidis* serogroups A, C, W and Y and not serogroup B is intended because administration of this combination vaccine exposes individuals to a reactogenic component that will not provide benefit unless the two-dose series is completed.
- Data were not provided that demonstrated effectiveness of a (b) (4) to prevent disease caused by all 5 serogroups to support a (b) (4) regimen of this combination vaccine.

9. Advisory Committee Meeting

Because all immunogens in this combination vaccine have preceded mechanisms of actions for the requested indication for use, and because review of this submission did not identify concerns that would have benefited from an advisory committee discussion, this submission was not discussed at a Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting.

10. Other Relevant Regulatory Issues

This application did not have any other major regulatory issues associated with it. This application was not granted priority or accelerated review and a priority review voucher was not redeemed.

11. Recommendations and Benefit/Risk Assessment

a. Benefit/Risk Assessment

PENBRAYA contains 5 of the 6 *N. meningitidis* serogroups (A, B, C, W, X, and Y) that cause meningococcal disease globally. *N. meningitidis* can cause invasive disease, which presents as septicemia, meningitis, or both. Adolescents and

young adults are one (1) of the age groups in which disease incidence is high compared to the general population.

Protection against invasive meningococcal disease is conferred mainly by complement-mediated antibody dependent killing by bactericidal antibodies specific to the capsular polysaccharides of *N. meningitidis* serogroups A, C, W, and Y and to fHbp present in the outer membrane of *N. meningitidis* serogroup B. Effectiveness was evaluated by measuring antibodies with assays that use human complement to assess serum bactericidal activity (hSBA). In study C4591001, noninferiority of hSBA responses was demonstrated for each serogroup after MenABCWY Dose 2 vs. Trumenba (MenB) Dose 2 (four MenB primary strains) and Menveo (MenACWY-CRM) Dose 1 (A,C,W,Y seroresponses).

The safety of MenACWY was evaluated in a total of 4546 individuals (2704 MenACWY, 1802 comparator) in 3 studies. The most commonly reported solicited adverse reactions after any dose were pain at the injection site (up to 89.3%), fatigue (up to 52.1%), headache (up to 46.8%), injection site redness (up to 25.9%), muscle pain (up to 25.7%), and injection site swelling (up to 25.0%). Except for injection site pain (6.5%–7.5%), rates of severe solicited adverse reactions were generally <3.0%. Fever ($\geq 38^{\circ}\text{C}$) was 5.9% after MenABCWY Dose 1, which was similar to the comparator group receiving MenB+MenACWY-CRM (5.8%). Across all studies, none of the SAEs, autoimmune or neuroinflammatory conditions after MenABCWY were assessed as related to vaccination by the study investigator or FDA/CBER clinical review team.

Risk mitigation strategies for MenABCWY use in individuals 10–25 years of age include communication of risks and benefits through labeling, including patient counseling information, and a pharmacovigilance plan to further evaluate risks. The Applicant committed to conduct a pregnancy registry study to evaluate the safety of MenABCWY vaccine exposure during pregnancy.

b. Recommended Regulatory Action

Based on the review of the clinical, nonclinical, and product-related data submitted in the original BLA, the Review Committee recommends approval of PENBRAYA for the labeled indication and usage.

c. Recommendation for Postmarketing Activities

Pfizer has committed to conduct the following postmarketing studies with milestone dates as shown as planned Postmarketing Requirements to fulfill PREA:

Pediatric Requirements

1. Deferred pediatric study under PREA (Study B1971067) to evaluate the safety and immunogenicity of MenABCWY in individuals 1 year to <10 years of age.

Final Protocol Submission: November 30, 2023

Study Completion Date: November 30, 2026

Final Report Submission: May 31, 2027

2. Deferred pediatric study under PREA (Study C3511005) to evaluate the safety and immunogenicity of MenABCWY in individuals 1 year to <10 years of age.

Final Protocol Submission: October 31, 2026

Study Completion Date: May 31, 2030

Final Report Submission: November 30, 2030

Postmarketing Commitments Subject To Reporting Requirements Under Section 506b

Pfizer has committed to conduct the following postmarketing study with milestone dates as shown as a planned Postmarketing Commitment to establish a pregnancy registry for PENBRAYA in the U.S. to collect and analyze the outcome of exposure to PENBRAYA during pregnancy and monitor for any potential safety signals that may arise in this population in routine public health settings.

3. A Pregnancy Registry Study to Evaluate the Safety of PENBRAYA Meningococcal Vaccine Exposure During Pregnancy

Final Protocol Submission: January 31, 2024

Study Completion Date: April 30, 2032

Final Report Submission: April 30, 2033

12. References

1. Goldschneider I, Gotschlich EC, Artenstein MS. Human immunity to the meningococcus. I. The role of humoral antibodies. *J Exp Med.* (1969);129:1307-1326.
2. Wang X, et al. Prevalence and genetic diversity of candidate vaccine antigens among invasive *Neisseria meningitidis* isolates in the U.S. *Vaccine* 2011; 29:4739-4744.