Summary Basis for Regulatory Action

Date:	June 17, 2024
From:	Tatiana Claro da Silva, PhD Review Committee Chair, OVRR/DRMRR
BLA STN:	125814/0
Parent [BLA/NDA] STN Note: this is only applicable if the STN will be merged with a Parent STN	N/A
Applicant:	Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc.
Submission Receipt Date:	October 18, 2023
Action Due Date:	June 17, 2024
Proper Name:	Pneumococcal 21-valent Conjugate Vaccine
Proprietary Name:	CAPVAXIVE
Indication:	For active immunization for the prevention of invasive disease caused by *Streptococcus pneumoniae (S. pneumoniae)* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B in individuals 18 years of age and older. For active immunization for the prevention of pneumonia caused by *S. pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B in individuals 18 years of age and older. The indication for the prevention of pneumonia caused by *S. pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B is approved under accelerated approval based on immune responses as measured by opsonophagocytic activity (OPA). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

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

Director, Product Office

Discipline Reviews	Reviewer / Consultant - Office/Division
CMC • CMC Product (Product Office and OCBQ/DBSQC) • Facilities review (OCBQ/DMPQ) • QC, Test Methods, Product Quality (OCBQ/DBSQC)	Shonoi Ming, PhD, OVRR/DBPAP Jiro Sakai, PhD, OVRR/DBPAP Debra Vause, OCBQ/DMPQ Hector Carrero, OCBQ/DMPQ Salil Ghosh, OCBQ/DBSQC Anil Choudhary, OCBQ/DBSQC Seth Schulte, OCBQ/DBSQC George Kastanis, OCBQ/DBSQC Ewan Plant, PhD, OVRR/DVP
Clinical • Clinical (Product Office) • Postmarketing safety Pharmacovigilance review (OBPV/DE) • BIMO	Nicholas Geagan, DO, OVRR/DCTR Sarah Benke, DO, OVRR/DCTR Victoria Moncada, OBPV/DPV Peter Lenahan, OCBQ/DIS
Statistical • Clinical data (OBPV/DB) • Non-clinical data	Trinetri Ghosh, PhD, OBPV/DB Yuan Hu, PhD, OBPV/DB Harry Houghton, PhD, OBPV/DB
Non-clinical/Pharmacology/Toxicology • Toxicology (Product Office) • Developmental toxicology (Product Office) • Animal pharmacology	Ching-Long (Joe) Sun, PhD, OVRR/DCTR
Clinical Pharmacology	
Labeling • Promotional (OCBQ/APLB)	Michael Brony, OCBQ/DCM Daphne Stewart, OVRR/DRMRR
Other Review(s) not captured above categories, for example: • Consults • Devices • Software • Human Factors • FONSI	Xinyi Ng, PhD, OBPV/DABRA Andrea Gray, PhD, ORO/DROP Brenda Baldwin, PhD, OVRR/DRMRR
Advisory Committee Summary	N/A

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1. Introduction

On October 18, 2023, Merck Sharp & Dohme LLC (Merck; the Applicant) submitted a biologics license application (BLA) for CAPVAXIVE; a 21-valent pneumococcal conjugate vaccine (PCV21; investigational product name V116). CAPVAXIVE contains capsular polysaccharides (PnPs) from *Streptococcus pneumoniae* (*S. pneumoniae*) serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B, as well as de-O-acetylated PnPs for serotype 15B (deOAc15B). The deOAc15B has a molecular structure similar to PnPs from serotype 15C, and the Applicant indicates that it induces an immunological response by cross-reactivity to serotypes 15B and 15C. Each pneumococcal capsular polysaccharide in the vaccine is covalently conjugated to carrier protein CRM197, a non-toxic mutant of diphtheria toxin. The vaccine dose is 0.5 mL, and it is supplied in a 1.5-mL pre-filled syringe (PFS) as a sterile liquid suspension for intramuscular (IM) injection. Throughout this document, the

tradename CAPVAXIVE will be used to identify the vaccine formulation used in clinical studies and intended for licensure.

Under this BLA, the Applicant is seeking approval for an indication for active immunization for the prevention of invasive pneumococcal disease (IPD) caused by *S. pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B in individuals 18 years of age and older.

The Applicant is also seeking an indication for the active immunization for the prevention of pneumonia caused by *S. pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B in individuals 18 years of age and older (pneumonia indication) using an accelerated approval (AA) pathway under 21 CFR 601.41. The rationale for AA is that CAPVAXIVE addresses a serious condition, i.e., pneumococcal pneumonia, and is expected to provide meaningful therapeutic benefit to patients over existing treatments.

The Applicant requested a priority review in their October 18, 2023, original submission. FDA granted priority review on December 15, 2023, with the justification that CAPVAXIVE meets the qualifying criteria as a drug that treats or prevents serious conditions (IPD and pneumonia) and provides a significant improvement in effectiveness over currently licensed pneumococcal conjugated vaccines.

The clinical program that supports CAPVAXIVE licensure in individuals 18 years of age and older under the current BLA includes results from four Phase 3 studies: V116-003, V116-004, V116-006, and V116-005, which are further discussed in the clinical section of this document. V116-003 was a randomized, double-blind study comparing the safety and immunogenicity of CAPVAXIVE with Prevnar 20 (PCV20) in vaccine-naïve individuals ≥18 years of age and was the pivotal effectiveness study supporting the IPD indication. Additionally, the immunogenicity data derived from V116-003 serves as the surrogate of efficacy for the pneumonia indication.

The primary objective of the Phase 3 studies above was evaluation of serotype-specific opsonophagocytic (OPA) responses, while evaluation of serotype-specific IgG geometric mean concentrations (GMCs) was a key secondary objective. Vaccine-induced, serotype-specific immune responses, OPA and IgG, were measured using validated multiplexed opsonophagocytic assay (MOPA) and pneumococcal electrochemiluminescence (Pn-ECL) assay, respectively. These immunogenicity results support approval of the IPD indication.

For the pneumonia indication, the Applicant proposed to use validated OPA results from study V116-003 as the primary endpoint and surrogate of efficacy for pneumococcal pneumonia for individuals 18 years of age and older that is likely to predict clinical benefit. In accordance with the AA regulations, adequate and well-controlled confirmatory studies to verify and describe clinical benefit must be conducted with due diligence to fulfill the regulatory requirements. The Applicant agreed to conduct a Phase 4 postmarketing observational real-world effectiveness (RWE) test negative design (TND) case control study titled "*A Test-Negative Case-Control Study to Evaluate the Effectiveness of V116 Against Pneumococcal Pneumonia in Older Adults*" as the confirmatory study to verify and describe clinical benefit of CAPVAXIVE against

pneumonia. The Applicant is expected to complete the design, implementation readiness verification, initiation, accrual, completion, and reporting of these studies within the framework described in their BLA submission.

CAPVAXIVE contains serotypes associated with adult pneumococcal disease that are not present in any currently licensed pneumococcal vaccine, i.e., serotypes 15A, 16F, 23A, 23B, 24F, 31, 35B, and deOAc15B which is structurally similar to 15C. The Center for Biologics Evaluation and Research (CBER) considers protection of individuals ≥18 years of age from pneumonia to be a meaningful therapeutic benefit over existing treatments.

Based on the review of the clinical, nonclinical, and product-related data submitted in the original BLA, and the TND postmarketing requirement (PMR) study required to confirm the effectiveness of CAPVAXIVE for pneumonia, the review committee recommends traditional approval of CAPVAXIVE for the IPD and AA for the pneumonia indications, following the labeled indication and usage.

2. Background

S. pneumoniae is a significant cause of morbidity and mortality among the elderly and persons who have certain underlying medical conditions. Pneumococcal disease can cause both invasive and non-invasive disease. Invasive pneumococcal disease (IPD) is defined by isolation of *S. pneumoniae* from a normally sterile site (e.g., blood, cerebrospinal, pleural, or peritoneal fluid) and can cause meningitis, bacteremia, sepsis, bacteremic pneumonia, and septic arthritis. The most common form of non-invasive disease, nonbacteremic pneumococcal pneumonia, remains a frequent manifestation accounting for pneumonia hospitalizations among adults worldwide.

Each *S. pneumoniae* serotype produces a chemically unique polysaccharide capsule. When administered in a vaccine, purified capsular polysaccharides are immunogenic, eliciting antibodies that are protective against pneumococcal disease. Pneumococcal polysaccharide vaccines specifically elicit a T-cell independent antibody response, with less robust immune responses observed in children under the age of 2 compared with older children and adults. Covalent conjugation of the pneumococcal polysaccharides to a carrier protein converts the immune response to a T-cell dependent response. T-cell dependent responses correlate with improved immunological memory in pneumococcal vaccine-naïve children, and compared with pneumococcal polysaccharide vaccines, pneumococcal conjugate vaccines (PCVs) generally elicit a stronger functional antibody response in older adults.

The impact of vaccination with PCVs is the reduction in incidence of disease caused by vaccine serotypes in the population targeted by the vaccination (primarily children <5 years of age in most countries) and the indirect effect in other age groups. However, while infant vaccination with PCVs has resulted in a decreased prevalence of IPD in the pediatric population, it has also led to increases in IPD due to serotypes not included in the licensed PCVs in several countries, particularly in adults, therefore resulting in an unmet medical need.

CAPVAXIVE is designed to provide significantly broader disease coverage against the leading serotypes associated with pneumococcal disease in adults compared with currently licensed pneumococcal vaccines, based, in part, on global serotype epidemiology data in older adults in regions with high pediatric vaccination uptake. CAPVAXIVE specifically targets residual disease in adults with the inclusion of key serotypes common to licensed vaccines and 8 unique serotypes not contained in any currently licensed vaccine.

S. pneumoniae is also a common cause of bacterial co-infection with influenza A. Bacterial co-infection commonly occurs within the first 6 days of influenza infection and is associated with an increased risk of death. Complex viral, bacterial, and host factors contribute to the pathogenesis of co-infection. Individuals at high risk of developing influenza-related complications including co-infection include adults ≥65 years of age and children <5 years of age.

Presently, there are four pneumococcal vaccines available in the U.S. for the prevention of pneumococcal disease in adults: 1) Pneumococcal Vaccine, Polyvalent (PPSV23 or V110; PNEUMOVAX 23), 2) Pneumococcal 13-valent Conjugate Vaccine (PCV13; PREVNAR 13), 3) Pneumococcal 15-valent Conjugate Vaccine (PCV15 or V114; VAXNEUVANCE) and 4) Pneumococcal 20-valent Conjugate Vaccine (PCV20; PREVNAR 20). The serotypes in bold below are common to CAPVAXIVE and the discussed vaccine.

PNEUMOVAX 23 (PPSV23) is a non-conjugated pneumococcal vaccine approved by the FDA in 1983 for active immunization for the prevention of pneumococcal disease caused by the 23 serotypes contained in the vaccine (1, 2, **3**, 4, 5, 6B, **7F**, **8, 9N**, 9V, **10A, 11A, 12F,** 14, ***15B***, **17F**, 18C, **19A**, 19F, ***20, 22***, 23F, and **33F**). It is currently approved for use in persons ≥50 years of age and persons ≥2 years of age who are at increased risk for pneumococcal disease. While the serotypes in bold above are common to PPSV23 and CAPVAXIVE, the latter contains a de-O-acetylated version of 15B. Moreover, additional serotype subtypes were identified after PPSV23 approval, and serotypes 20 and 22 are characterized as 20A and 22F in CAPVAXIVE.

PREVNAR 13 (PCV13), a 13-valent pneumococcal conjugate vaccine and a successor of Prevnar (PCV7), is approved for use in children ages 6 weeks through 5 years as a four-dose immunization series, children 6 through 17 years of age as a single dose, and individuals 18 years and older as a single dose. PREVNAR 13 is composed of 13 serotypes of *S. pneumoniae* (1, **3**, 4, 5, **6A**, 6B, **7F**, 9V, 14, 18C, **19A**, 19F, and 23F) individually conjugated to CRM197. PREVNAR 13 contains aluminum phosphate as an adjuvant and is administered intramuscularly. It was approved in December 2011 under AA regulations (21 CFR 601.41) for active immunization for the prevention of IPD and pneumonia caused by the 13 serotypes contained in the vaccine in persons ≥50 years of age based on a serological endpoint (OPA antibody titer). As a condition of AA, the manufacturer completed a postmarketing study that confirmed and described the efficacy of PREVNAR 13 for the approved indications. In 2016, FDA approved a supplemental BLA application to expand the usage of PCV13 for the approved indications to adults 18 through 49 years of age based on immunologic bridging studies.

VAXNEUVANCE (PCV15) was approved in July 2021, for the active immunization for the prevention of IPD caused by *S. pneumoniae* serotypes 1, **3**, 4, 5, **6A**, 6B, 7F, 9V, 14, 18C, **19A**, 19F, **22F**, 23F and **33F** in individuals 6 weeks of age and older.

PREVNAR 20 (PCV20) was approved in July, 2021, for active immunization for the prevention of IPD caused by *S. pneumoniae* serotypes 1, **3**, 4, 5, **6A**, 6B, **7F**, **8**, 9V, **10A**, **11A**, **12F**, 14, ***15B***, 18C, **19A**, 19F, **22F**, 23F, and **33F** in individuals 6 weeks of age and older; prevention of otitis media caused by serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F in individuals 6 weeks through 5 years of age; pneumonia caused by serotypes 1, **3**, 4, 5, **6A**, 6B, **7F**, 8, 9V, **10A**, **11A**, **12F**, 14, **15B**, 18C, **19A**, 19F, **22F**, 23F, and **33F** in individuals 18 years of age and older. The indication for the prevention of pneumonia caused by serotypes 8, **10A**, **11A**, **12F**, ***15B***, **22F**, and **33F** is approved under AA based on immune responses as measured by OPA assay. Continued approval for this indication is contingent upon verification and description of clinical benefit in a postmarketing confirmatory study.

Approval of CAPVAXIVE for the prevention of pneumonia in adults caused by the serotypes in the vaccine is based on an immunologic surrogate endpoint (OPA titer) that is reasonably likely to predict prevention of pneumococcal pneumonia caused by CAPVAXIVE vaccine serotypes, as afforded by AA regulations (21 CFR 601.41). This regulation applies to biologics intended to treat or prevent serious or life-threatening illnesses, and which provide meaningful therapeutic benefit to patients over existing treatments (21 CFR 601.40). Pneumococcal pneumonia is a serious condition and CAPVAXIVE is designed with serotypes associated with residual pneumococcal disease in adults, including 8 serotypes not included in other approved vaccines. It is expected to provide meaningful therapeutic benefit to patients over existing treatments. Therefore, the proposed indication meets the qualifying criteria for AA. The initial draft protocol for the postmarketing confirmatory RWE study was received on July 7, 2022, and CBER's comments dated August 30, 2022; March 14, 2023; September 19, 2023; November 17, 2023; December 22,2023; February 1 and February 7, 2024, were incorporated into a revised draft protocol which was submitted to this BLA.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
1. Pre-IND meeting (PS004923)	Aug 15, 2019
2. IND submission (IND 19316)	October 15, 2019
3. Fast Track designation granted (IND 19316)	December 13, 2019
4. Orphan Drug designation granted (if applicable)	N/A
5. Breakthrough Therapy designation granted (if applicable)	January 10, 2022
6. Pre-BLA meeting	September 19, 2023
7. Rare Pediatric Disease designation granted (if applicable)	N/A
8. BLA 125814/0 submission	October 18, 2023
9. BLA filed	December 15, 2023
10. Mid-Cycle communication	February 7, 2024
11. Late-Cycle meeting	March 21, 2024
12. Major Amendment (if applicable)	N/A
13. Complete Response (if applicable)	N/A
14. Re-submission after Complete Response (if applicable)	N/A
15. Action Due Date	June 17, 2024

Source: FDA-generated table

3. Chemistry Manufacturing and Controls (CMC)

a. Product Quality

CAPVAXIVE is supplied in 1.5-mL pre-filled syringes (PFSs) as a 0.5 mL single-dose solution for IM administration. The Drug Product (DP) is a sterile solution of purified PnPs from 21 *S. pneumoniae* serotypes individually conjugated to CRM197 carrier protein, a nontoxic mutant of diphtheria toxin expressed recombinantly in *Pseudomonas fluorescens*. The PnPs in the vaccine originated from serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, 35B and 15B (de-O-acetylated prior to conjugation).

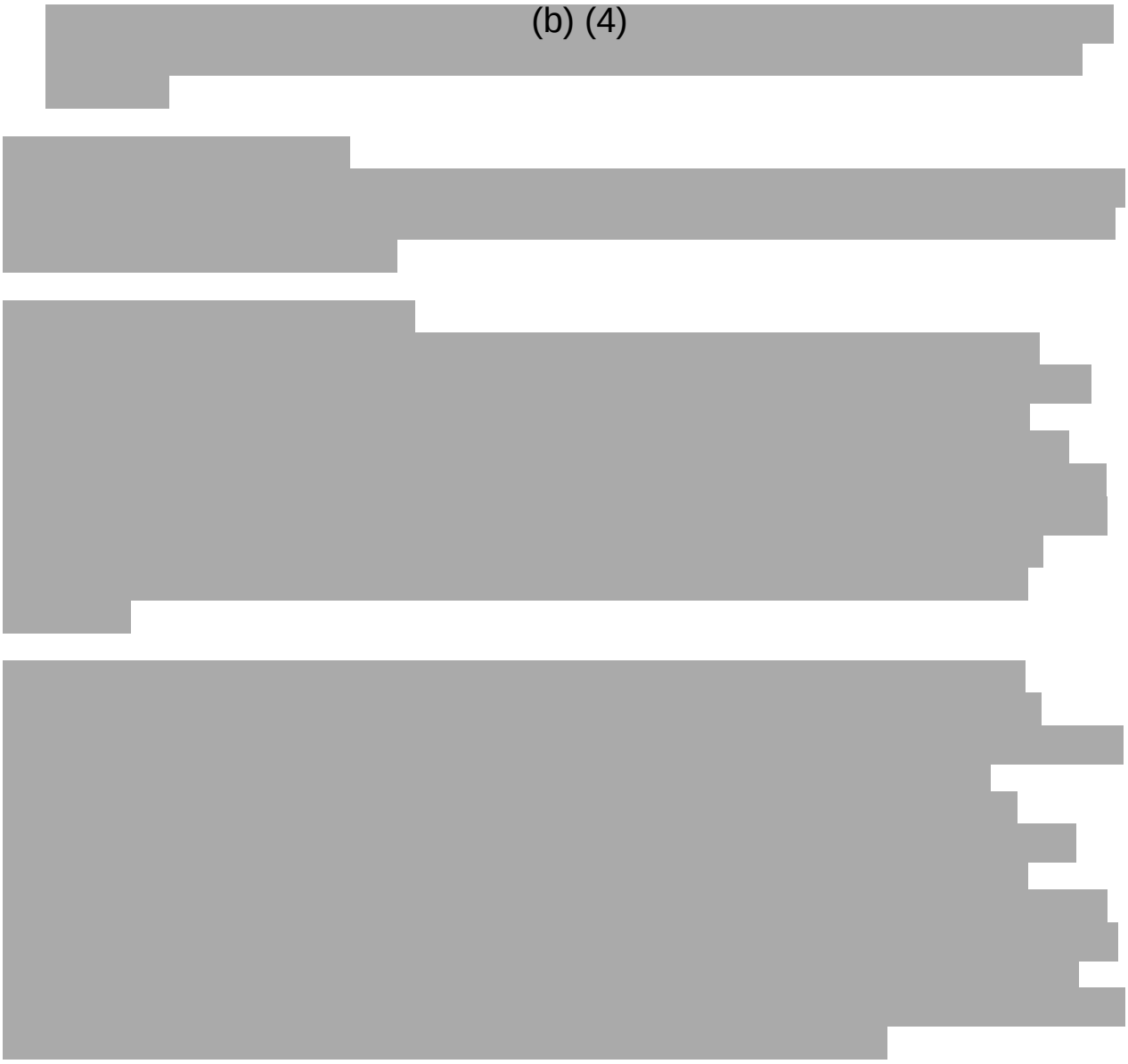
The PnPs (b) (4) are produced at Merck's (b) (4) site. CRM197 is manufactured at (b) (4). The 21 (b) (4) Conjugates (b) (4) are produced at Merck's (b) (4) site, and the DP is produced at Merck's (b) (4) site.

Drug Substances

(b) (4)

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

(b) (4)



Drug Product

The final drug product (DP) is composed of a mixture of the 21 conjugated drug substances ((b) (4) serotypes mentioned previously) in a sterile liquid solution in 1.5-mL glass, Luer-lock, prefilled syringes for IM administration. A 0.5-mL dose was selected for Phase 3 and Process Performance Qualification (PPQ) batches to align with the injection volume of the Applicant's related products.

Each 0.5 mL dose of CAPVAXIVE DP contains a total of 84 mcg of purified PnPs antigens (4 mcg of PnPs from each of the serotypes), approximately 65 mcg of CRM197 carrier protein, 1.55 mg L-histidine, 0.50 mg of polysorbate 20, 4.49 mg sodium chloride, and water for injection. The DP is sterile filtered as it is filled into a 1.5-mL glass syringe barrel assembly and stoppered with a plunger stopper to make a PFS and deliver a nominal dose of 0.5 mL. The DP is stored at 2–8°C and does not contain any preservatives.

Formulation and Filling

The DP is manufactured by (b) (4) The (b) (4) is sterile filtered into syringes and the plunger stopper set in place automatically. Each syringe is transferred to the Automated Inspection Machine for 100% visual inspection for defects. After inspection the syringes are stored in (b) (4) at 2–8°C in preparation for packaging and labeling.

Tests performed at release for the DP include (b) (4) testing where appropriate. Bioburden, endotoxin, and filter (b) (4) testing are performed (b) (4) and (b) (4) filling. The PPQ demonstrates that the formulation and fill processes for CAPVAXIVE DP are capable of reliably producing consistent product.

Release and Stability

The Applicant established the CAPVAXIVE DP release and stability acceptance criteria in consideration of (b) (4) and commercial-scale manufacturing experience.

Table 2. Release and Stability Specifications, Drug Product

Attribute	Acceptance Criteria – Release	Acceptance Criteria – Stability	Test Method
Appearance (Degree of Coloration)	Colorless	Colorless	(b) (4)
Appearance (Opalescence)	Clear to Opalescent	Clear to Opalescent	
(b) (4)	(b) (4)	(b) (4)	
Identity	Presence of Serotype-Specific Polysaccharides Confirmed	NA	
Saccharide Content (µg/mL)	All Serotypes: (b) (4)	All Serotypes: (b) (4)	
Conjugated Saccharide Content (µg/mL): Serotypes 23B, 24F	(b) (4)	(b) (4)	
Conjugated Saccharide Content (µg/mL): Serotypes 15B, 19A, 23A, 35B	(b) (4)	(b) (4)	
Conjugated Saccharide Content (µg/mL): All Other Serotypes	(b) (4)	(b) (4)	
(b) (4)	Calculated	Calculated	
Polysorbate-20 Content (b) (4)	(b) (4)	NA	
(b) (4)	(b) (4)	(b) (4)	
(b) (4)	(b) (4)	(b) (4)	
Recoverable Volume (mL)	0.50 (b) (4)	0.50 (b) (4)	
Syringeability	Liquid is dispensed from the needle in an even stream; no evidence of needle blockage	Liquid is dispensed from the needle in an even stream; no evidence of needle blockage	
Syringe Functionality (b) (4)	NA	(b) (4)	
Endotoxin (b) (4)	(b) (4)	NA	
Sterility	No Growth	No Growth	
Container Closure Integrity	NA	(b) (4)	

Storage, Shelf Life, and Shipping

The DP is stored at 2–8°C as a solution in PFS with a proposed shelf life of 18 months, which is supported by the information submitted to the file. All stability results remained within the commercial acceptance criteria and exhibited no observable change in quality for the CAPVAXIVE DP in the PFS when stored at (b) (4) to support unplanned excursions to these temperatures. The photostability

study demonstrated that the market package provided CAPVAXIVE DP syringes with appropriate protection from the effects of light exposure specified in ICH Q1B, and that nude syringes support the recommended storage to “Protect from Light.”

The Applicant committed to continue any ongoing stability studies to support the DP shelf life at the long-term storage condition.

CMC Comparability Assessment

The following comparability protocols are included in the BLA:

- Post-approval change management protocol for reference standards for drug product (DP): This comparability protocol (CP) describes the plan for the introduction of new DP primary and secondary reference standards, i.e., primary reference standard (PRS) and secondary reference standard (SRS), respectively. The CP also includes the plan for the shelf-life extension of the SRS. Merck will report the extension of shelf-life of the SRS and the introduction of new SRS in an annual report. The introduction of new PRS will be submitted in a CBE-30.

- Post-approval change management protocol for reference standards for drug substance (DS): This CP describes the plan for the introduction of new DS reference standards used to determine (b) (4) . The CP also includes the plan for extension of shelf-life for the reference standard. Merck will report the extension of shelf-life and introduction of new reference standard in an annual report.

Combination Product

CAPVAXIVE is considered a combination product; thus, a CBER device reviewer evaluated the PFS component. Based on the information provided in the application and subsequently during review, as well as in the cross-referenced master files, the reviewer recommended approval.

b. Testing Specifications

The analytical methods and their validations and/or qualifications reviewed for the CAPVAXIVE DSs and DP 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 Pneumococcal

21-valent conjugate vaccine are listed in the table below. The activities performed and inspectional histories are noted in the table.

Table 3. Manufacturing Facilities, Pneumococcal 21-Valent Conjugate Vaccine

Name/Address	FEI number	DUNS number	Inspection /Waiver	Justification /Results
Merck Sharp & Dohme LLC (Merck (b) (4)) (b) (4) DS intermediate manufacturing, Combination Product Assembly, Primary Labeling, Finished Product Release	(b) (4)	(b) (4)	Waiver	ORA/OBPO (b) (4) VAI
(b) (4) DS intermediate manufacturing	(b) (4)	(b) (4)	Waiver	ORA/OBPO (b) (4) NAI
MSD (b) (4) DS manufacturing and DP Release Testing	(b) (4)	(b) (4)	Waiver	ORA/OBPO (b) (4) NAI
MSD (b) (4) DP manufacturing and DP Release Testing	(b) (4)	(b) (4)	Waiver	ORA/OBPO (b) (4) VAI
(b) (4) DP Release Testing	(b) (4)	(b) (4)	Waiver	ORA (b) (4) VAI
Merck Sharp & Dohme LLC (b) (4) Primary Labeling, Combination Product Assembly, Finished Product Release	(b) (4)	(b) (4)	Waiver	ORA/OBPO (b) (4) NAI

Abbreviations: CBER=Center for Biologics Evaluation and Research; OBPO=Office of Biological Products Operations; ORA=Office of Regulatory Affairs; DS=drug substance; DP=drug product; NAI=No Action Indicated; VAI=Voluntary Action Indicated.

ORA/OBPO performed a surveillance inspection of the Merck (b) (4) manufacturing facility in (b) (4) , and the inspection was classified as VAI.

ORA/OBPO performed a surveillance inspection of the (b) (4) manufacturing facility in (b) (4) . A Form FDA 483 list of observations was not issued, and the inspection was classified as NAI.

ORA/OBPO performed a surveillance inspection of the MSD (b) (4) manufacturing facility in (b) (4) . A Form FDA 483 list of observations was not issued, and the inspection was classified as NAI.

ORA/OBPO performed a surveillance inspection of the MSD (b) (4) manufacturing facility in (b) (4) , and the inspection was classified as VAI.

ORA performed a surveillance inspection of the (b) (4) manufacturing facility in (b) (4), and the inspection was classified as VAI.

ORA/OBPO performed a surveillance inspection of the Merck (b) (4) manufacturing facility in (b) (4). A Form FDA 483 list of observations was not issued, and the inspection was classified NAI.

e. Container/Closure System

The Pneumococcal 21-valent conjugate vaccine drug product (DP) is provided as a single-dose pre-filled syringe (PFS) with no preservative. The combination product is defined as the filled and stoppered syringe barrel assembly, with the plunger rod inserted. The primary packaging and combination product components used for the vaccine are described in the table below. The primary components are sterilized before use. Merck conducted the container closure integrity testing (CCIT) employing (b) (4); all acceptance criteria were met.

Component	Description
Syringe Barrel	• (b) (4) 1.5 mL Type (b)(4) glass barrel with Luer -Lock adapter. Barrel lubricated with (b) (4). Polypropylene rigid tip cap with (b) (4) 0 product contact component made of styrene butadiene. • (b) (4) 1.5 mL Type (b)(4) glass barrel with Luer Lock adapter. Barrel lubricated with (b) (4). Polypropylene rigid tip cap with (b) (4) product contact component made of synthetic isoprene bromobutyl.
Plunger Stopper	(b) (4) plunger stopper with a fluoropolymer lamination; not made with natural rubber latex.

f. Environmental Assessment

The BLA/NDA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31. FDA concluded that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

Nonclinical Toxicology

The sponsor submitted study reports of a 22-day intramuscular toxicity study in rats and a reproductive toxicity study in rats. In both cases, animals were dosed intramuscularly with a conjugated polysaccharide vaccine formulation containing the same conjugated polysaccharides as in CAPVAXIVE (V116) and received 42 mcg (2 mcg for each of the 21 serotypes) polysaccharide per dose (a full human dose of CAPVAXIVE contains 84 mcg polysaccharide/dose). The intramuscular toxicity study had been submitted and reviewed in the original IND 19316, in 2019. In that study, animals were dosed with 0.5 mL of the formulation containing 42 mcg polysaccharides. The findings were typical local inflammatory reactions at the injection sites. All the findings at the injection site were reversible. In the reproductive toxicity study, two groups of 44 female rats were administered control article (phosphate buffer) or the vaccine formulation (with

(b) (4) buffer as one of the excipients) on four occasions: 28 and 7 days prior to mating, on gestation day 6, and on lactation day 7. The animals in each group were divided into cohort 1 (cesarean-sectioning phase) and cohort 2 (natural delivery phase). Cohort 1 animals were euthanized on gestation day 21. Cohort 2 animals were allowed to deliver naturally and euthanized on lactation day 21. There were no effects on mating performance, or fetal weight, or any naturally delivery or litter parameters, or any fetal external, visceral or skeletal malformations. Injection of the vaccine formulation led to development of CAPVAXIVE serotype-specific antibodies present in female rats and their offspring. Based on the results, the vaccine was immunogenic in animals and there was evidence of placental transfer.

Pharmacological findings

Immunogenicity in mice and adult (b) (4) monkeys
Merck evaluated immunogenicity of CAPVAXIVE in mice and adult (b) (4) monkeys. V116 elicited IgG antibodies against all 21 serotypes, functional antibodies against all 21 serotypes, and protected mice from lethal intratracheal challenge with *S. pneumoniae* serotype 24F. Assessment of IgG and OPA titers suggested cross-reactivity between 6A and 6C. Similarly, comparable IgG and OPA titers between 15B and 15C also suggested cross-reactivity between these serotypes. Adult (b) (4) monkeys received V116 alone at Days 0, 28 and 56 (V116 ARM-1) or in parallel with other pneumococcal vaccines, namely, V114, PCV13, and PPSV23, at Day 0 (V116 ARM-3). V116 was immunogenic, generated functional antibodies, and had comparable immunogenicity to all three comparator vaccines for shared serotypes.

Studies in mice also demonstrated consistency of responses between two lots of V116, with comparable IgG antibody responses.

5. Clinical Pharmacology

Protection against IPD is conferred mainly by opsonophagocytic killing of *S. pneumoniae*. CAPVAXIVE induces OPA against 22 *S. pneumoniae* serotypes. The de-O-acetylated polysaccharide from serotype 15B has a molecular structure similar to serotype 15C and induces OPA to serotype 15C. The deOAc15B also induces cross-reactive OPA against serotype 15B. An OPA titer that is predictive of protection against IPD or pneumococcal pneumonia has not been established.

6. Clinical/Statistical

a. Clinical Program

The Applicant has submitted data from five clinical studies as part of this BLA, including four Phase 3 trials which provided the principal data to support the safety and effectiveness of CAPVAXIVE for the intended indication in individuals 18 years of age and older, as well as clinical data to support manufacturing consistency (lot consistency). These four trials (V116-003, V116-004, V116-006, and V116-005) enrolled adults with and without prior history of pneumococcal vaccination. Study V116-003 (Study 003), which enrolled pneumococcal vaccine-naïve individuals ≥18 years of age, evaluated immunogenicity and safety of a single dose of CAPVAXIVE compared with

Prevnar 20 (PCV20; Wyeth Pharmaceuticals) and immunobridging participants 18 through 49 years of age with participants ≥50 years of age. Study V116-004 (Study 004) evaluated lot-to-lot consistency in pneumococcal vaccine-naïve individuals 18 through 49 years of age. Study V116-006 (Study 006) enrolled pneumococcal vaccine-experienced individuals 50 years of age and older and evaluated safety and immunogenicity of CAPVAXIVE compared to active control [Vaxneuvance (PCV15; Merck Sharp & Dohme) or Pneumovax 23 (PPVS23; Merck Sharp & Dohme)]. Study V116-005 (Study 005) evaluated the safety and immunogenicity of CAPVAXIVE when administered concomitantly with a quadrivalent influenza vaccine compared to sequential administration in pneumococcal vaccine-naïve individuals 50 years of age and older.

Immunogenicity Analyses:
Immunogenicity of CAPVAXIVE was evaluated in Study 003, a Phase 3, randomized, active comparator-controlled, double-blind, international clinical trial. A total of 2,663 participants (1382 CAPVAXIVE, 1281 PCV20) enrolled in the study. The co-primary objectives were to establish effectiveness of CAPVAXIVE in individuals ≥50 years of age through serotype-specific OPA and to establish effectiveness in individuals 18 through 49 years of age by comparison with individuals ≥50 years of age through OPA. The primary endpoint in individuals 50 years of age was serotype-specific OPA geometric mean titers (GMTs) at 30 days postvaccination. The predefined noninferiority success criteria (lower bound of 95% CI of the OPA GMT ratio [CAPVAXIVE/PCV20] >0.5) were met for the 10 common serotypes. The predefined criteria for statistically significantly higher OPA responses (LB of the 95% CI of the OPA GMT ratio >2.0) compared with PCV20 were met for 10 of 11 serotypes unique to CAPVAXIVE. For serotype 15C, the LB of the 95% CI of the OPA GMT ratio was 1.77. The predefined criteria for immunobridging were met for CAPVAXIVE in participants 18 through 49 years of age compared with CAPVAXIVE in participants 50 through 64 years of age for all 21 serotypes as assessed by serotype-specific OPA GMTs (lower bound of the 95% CI of the OPA GMT >0.5) at 30 days postvaccination.

Analyses of secondary outcomes included evaluations of OPA responses for serotypes 15B and 6C, which are not included in the vaccine formulation, but for which OPA responses to CAPVAXIVE were assessed based on antigenic similarity with vaccine serotypes (i.e., 15C[1] and 6A). For serotype 15B, CAPVAXIVE met the predefined criterion for antibody response (lower bound of 95% CI of the percentage of participants with a ≥4-fold rise in OPA responses >50%) with the percentage of participants with a ≥4-fold rise in OPA responses from baseline to 30 days postvaccination being 64.7% (95% CI: 61.4, 67.8). For serotype 6C, CAPVAXIVE did not meet the predefined criterion for antibody response with the percentage of participants with a ≥4-fold rise in OPA responses from baseline to 30 days postvaccination being 49.3% (95% CI: 46.0, 52.6).

Study 004 was designed as a lot-to-lot consistency, immunogenicity, and safety study in individuals 18 through 49 years of age. Pneumococcal vaccine-naïve individuals 18 through 49 years of age received a single dose from one of three CAPVAXIVE lots or PPSV23. The equivalence criteria were met for all 21 serotypes in CAPVAXIVE,

1 CAPVAXIVE contains de-O-acetylated polysaccharide from serotype 15B [deOAc15B], which is similar in structure to polysaccharide from 15C. The antibody response to deOAc15B is measured as serotype 15C.

demonstrating lot-to-lot equivalency and providing clinical evidence of manufacturing consistency.

Study 006 was designed to descriptively evaluate the safety and immunogenicity of CAPVAXIVE in pneumococcal vaccine-experienced individuals ≥50 years of age compared with an active U.S.-licensed control vaccine (PCV15 or PPSV23) for 2 of the 3 cohorts. Across all 3 cohorts, CAPVAXIVE was immunogenic for all 21 serotypes contained in the vaccine as assessed by serotype-specific OPA GMTs at 30 days postvaccination.

Study 005 was a Phase 3, randomized, double-blind, placebo-controlled study in which immunogenicity was assessed for CAPVAXIVE when administered concomitantly with a quadrivalent influenza vaccine (QIV) compared with when administered sequentially. Except for pneumococcal serotype 23B and influenza strain A/H3N2, the primary objectives to demonstrate noninferiority of concomitant administration of CAPVAXIVE and QIV were met (LB of the 95% CI of the GMT ratio >0.5 and >0.67, respectively) compared with pneumococcal and influenza antibody responses following sequential administration. For pneumococcal serotype 23B and influenza strain A/H3N2, the LB of the 95% CI of the group GMT ratio was 0.44 and 0.67, respectively.

CAPVAXIVE demonstrated effectiveness against IPD for 22 pneumococcal serotypes based on OPA responses. Across the Phase 3 studies, CAPVAXIVE was noninferior to active, U.S.-licensed comparators for the shared serotypes and 15B, and statistically superior to the unique serotypes with the exception of 15C which marginally missed the pre-defined success criterion. The totality of data supports licensure of CAPVAXIVE for the indication of active immunization for the prevention of IPD caused by the specified serotypes.

Safety
The safety of CAPVAXIVE after a single dose was evaluated in four Phase 3 studies (4,020 received CAPVAXIVE, 2018 received active control). Solicited adverse reactions within 5 days of vaccination (Study 003) occurred at similar rates between CAPVAXIVE and PCV20 (55.3% CAPVAXIVE, 61.3% PCV20). In both groups there was a trend towards higher rates of reactions in the 18 through 49 years of age group. The most frequently reported local reaction in all groups was pain at the injection site (Cohort 1: 39.4% CAPVAXIVE, 51.7% PCV20; Cohort 2: 71.5% CAPVAXIVE, 74.0% PCV20) and the most frequently reported systemic reaction was fatigue (Cohort 1: 20.1% CAPVAXIVE, 19.6% PCV20; Cohort 2: 40.5% CAPVAXIVE, 34.0% PCV20). Severe (Grade 3) solicited local and systemic reactions were reported in 0.5% of CAPVAXIVE recipients in Cohort 1, 1.0% of PCV20 recipients in Cohort 1, 4.5% of CAPVAXIVE recipients in Cohort 2, and 3.0% of PCV20 recipients in Cohort 2. The percentage of vaccine recipients that reported at least one unsolicited, non-serious adverse event (AE) through 1-month postvaccination was 22.3% in CAPVAXIVE recipients and 22.2% in active control recipients.

The percentage of participants reporting at least one non-fatal serious adverse event (SAE) in the 4 Phase 3 studies was 1.4% among CAPVAXIVE recipients and 2.0% of comparator recipients. Two SAEs were assessed to be related to the study vaccination: one participant in study 005 with reported bronchospasm and one participant in study

006 who reported injection-site cellulitis (See individual studies in section 6 for narrative details). Deaths were reported for 6 CAPVAXIVE recipients (0.1%) and 3 active comparator recipients (0.1%). Based on independent review of event narratives, FDA considers the deaths to be either attributable to the participants underlying medical conditions, risk factors, concurrent medical conditions, or events that are not physiologically plausible to be attributed to vaccination. There were no SAEs or deaths observed in the Phase 1/2 study that could be attributed to vaccination.

The data submitted to this BLA support the safety of CAPVAXIVE when administered to individuals ≥18 years of age. The SAE rates among CAPVAXIVE and active comparators (PCV20, PPSV23, or PCV15) were similar and were ≤2.0%. Two SAEs (bronchospasm, injection site cellulitis) were assessed to be related to CAPVAXIVE vaccination. No additional safety concerns were identified when a single dose of CAPVAXIVE was administered to individuals ≥18 years of age, with or without prior pneumococcal vaccine exposure.

Pneumococcal Pneumonia Indication
Vaccine effectiveness of CAPVAXIVE to prevent pneumococcal pneumonia in individuals ≥18 years of age was based on a immunological surrogate endpoint (OPA GMT) reasonably likely to predict clinical benefit (21 CFR 601.41). As a condition of accelerated approval, the Applicant will conduct a postmarketing real-world effectiveness study as a confirmatory study to verify and describe clinical benefit of CAPVAXIVE for the prevention of serotype-specific pneumococcal pneumonia.

Serology

The OPA assay provides an *in vitro* measurement of the ability of serum antibodies to eliminate pneumococci by promoting complement-mediated phagocytosis and is believed to reflect relevant *in vivo* mechanisms of protection against IPD. OPA titers are expressed as the reciprocal of the highest dilution that results in ≥50% bacterial killing. There is no accepted immunological threshold level of antibody concentration that correlates with protection against IPD in adults. Opsonophagocytic antibodies are surrogate markers for vaccine efficacy against IPD and have been shown to correlate with vaccine-induced protection. Nonclinical and clinical data support CAPVAXIVE immunogenicity, as measured by OPA assay. Multiplexed OPA (MOPA) was used for measuring the functionality of vaccine-induced antibodies against each of the 21 serotypes contained in CAPVAXIVE in the primary endpoint of the Applicant's Phase 3 clinical studies. The CAPVAXIVE immunogenicity for serotypes 6C and 15B was not tested in the prespecified primary endpoint.

IgG antibody levels were a secondary endpoint in these studies. The Applicant used the pneumococcal electrochemiluminescence (Pn-ECL) assay to assess IgG responses (geometric mean IgG concentrations). The ECL method measures anti- PnPs antibodies against serotypes 3, 6A, 6C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 15B, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B. The Pn-ECL assay is based on Meso-Scale Discovery (MSD) technology enabling simultaneous detection of anti-PnPs antibodies for multiple serotypes in serum.

MOPA and Pn-ECL were validated to support their use in the Phase 3 studies. MOPA was validated in terms of ruggedness and precision, relative accuracy/dilutional linearity, analytical specificity, and matrix interference. (b) (4) assay was performed to screen serum samples from clinical studies for intrinsic, antibody-independent killing prior to the evaluation of functional antibodies of serum samples in MOPA. Pn-ECL was validated in terms of precision, assay ruggedness, selectivity, specificity, and dilutional linearity. All assays are adequate for their intended uses to evaluate primary and secondary clinical endpoints.

The Applicant also provided data to support that the MOPA and Pn-ECL assays performed consistently during the clinical testing period, from assay validation through the Phase 3 studies. Review of the data showed no deficiencies.

The Applicant is developing the high-throughput multiplex Serotype-Specific Urinary Antigen Detection (SSUAD) and the Pneumococcal Antigen Detection assay (PAD) assays, which they will use to measure serotype-specific PnPs in urine and blood samples, respectively, collected from patients enrolled in the Phase 4 TND RWE study to support traditional approval for their pneumonia indication after AA under the current original BLA. The SSUAD and PAD assays will be further reviewed under future submissions to the IND as development continues. Their current state of development does not prevent the approval of this BLA. The Applicant committed to submit validation protocols by November 1, 2024, and validation packages by May 30, 2025. These milestones are included in the Approval letter.

The Applicant compared the immunogenicity and safety of CAPVAXIVE when administered concomitantly with inactivated quadrivalent influenza vaccine in individuals 50 years of age or older, in study V116-005. The Hemagglutination Inhibition (HI) assay was used to measure antibody responses toward influenza antigens. Review of the data indicated that the HI assay is suitable for determining serum antibody titers toward influenza strains included in the vaccines used in the concomitant use study V116-005.

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

Bioresearch Monitoring (BIMO) inspections were issued for two domestic and two foreign clinical investigators who participated in the conduct of Protocol V116-003. The inspections did not reveal substantive issues that impact the data submitted in this original Biologics License Application (BLA).

c. Pediatrics

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. Under PREA, the submission of this original BLA required a Pediatric Study Plan for the claimed indications.

The safety and effectiveness of CAPVAXIVE have not been established in individuals younger than 18 years of age. The Applicant requested a full waiver of the pediatric

study requirement in persons from birth through <18 years of age for the pneumonia indication, because the necessary studies are impossible or highly impracticable (505B(a)(4)(A)(i) of the Act). The Applicant requested a partial waiver of the pediatric study requirement in infants from birth to <2 years of age for the IPD indication because CAPVAXIVE does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and CAPVAXIVE is not likely to be used by a substantial number of pediatric patients in this age group (505B(a)(5)(B)(iii) of the Act). The Applicant requested a deferral of pediatric studies in persons 2 years through <18 years of age with underlying risk factors that predispose to an increased risk of IPD to support the IPD indication on the basis that CAPVAXIVE is ready for approval for use in adults before pediatric studies are complete. (505B(a)(4)(i)(I) of the Act).

The Pediatric Study Plan was presented to FDA's Pediatric Review Committee (PeRC) on July 5, 2022, under IND 19316. The PeRC agreed with the Pediatric Study Plan, including the full waiver, partial waiver and deferral requests and the proposed timelines for each protocol submission, study completion and report submission. The agreed iPSP was included in the current BLA.

The deferred pediatric study required under 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) is a required postmarketing study; the agreed study and timeline are described in section 11.C of this document.

d. Other Special Populations

Not Applicable

7. Safety and Pharmacovigilance

The Applicant's Pharmacovigilance Plan (PVP) adequately reflects the safety concerns based on the clinical trial experience. There are no important identified or potential risks in the Applicant's proposed PVP. This risk assessment is consistent with the safety profile observed in the clinical trials, for which there were no concerning differences in rates of SAEs, very few SAEs (one event each of bronchospasm and injection-site cellulitis) and no deaths that were attributed to vaccination with CAPVAXIVE. Other populations discussed (other immunocompromised, pregnancy/lactating individuals) do no warrant inclusion in the PVP at this time. The reviewed data do not indicate a safety signal which would require either a Risk Evaluation and Mitigation Strategy (REMS), or a postmarketing commitment (PMC) or postmarketing requirement (PMR) study that is specifically designed to evaluate safety as a primary endpoint.

8. Labeling

The proposed proprietary name, CAPVAXIVE, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on January 11, 2024, and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on January 23, 2024.

The Advertising and Promotional Labeling Branch (APLB) reviewed the proposed Prescribing Information (PI), Patient Packet Insert, and package and container labels, on

March 15, 2024, and found them acceptable from a promotional and comprehension perspective.

The review team negotiated revisions to the PI. All labeling issues regarding the PI and the carton and container labels were resolved following the exchange of information and discussions with the Applicant.

9. Advisory Committee Meeting

This submission was not discussed at a Vaccines and Related Biological Products Advisory Committee meeting because FDA review of this submission did not identify concerns or issues which would have benefited from an advisory committee discussion.

10. Other Relevant Regulatory Issues

On December 15, 2023, FDA granted priority review designation for the BLA.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

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

b. Benefit/Risk Assessment

Considering the data submitted to support the safety and efficacy of CAPVAXIVE that have been presented and discussed in this document, the Review Committee is in agreement that the risk-benefit profile for CAPVAXIVE is favorable and supports approval for use in individuals 18 years of age and older for the prevention of vaccine-type IPD (traditional approval) and vaccine-type pneumococcal pneumonia (accelerated approval).

c. Recommendation for Postmarketing Activities

The Applicant's proposed pharmacovigilance plan is adequate. The available safety data do not substantiate a need for a Risk Evaluation and Mitigation Strategy (REMS) or a safety-related postmarketing requirement or commitment (PMR/PMC) study.

The Applicant has committed to conduct the following required postmarketing activities which are specified in the approval letter for this application.

Required Pediatric Assessments

If your application is approved, under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and

effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

The following proposed deferred pediatric studies are agreed upon by the Agency:

1. To conduct a deferred pediatric study under PREA to evaluate the safety and immunogenicity of CAPVAXIVE in children and adolescents 2 to <18 years of age.

   Final Protocol Submission: July 31, 2024
   Study Completion Date: June 30, 2026
   Final Report Submission: December 31, 2026

Confirmatory Clinical Studies to Verify Clinical Benefit (PMRs)
In accordance with the accelerated approval regulations, adequate and well-controlled confirmatory studies to verify and describe clinical benefit must be conducted with due diligence to fulfill the regulatory requirements.

To verify clinical benefit, the Applicant submitted a protocol *"A Test-Negative Case-Control Study to Evaluate the Effectiveness of V116 Against Pneumococcal Pneumonia in Older Adults"* (V116-011-00-v2) for a real-world evidence (RWE), multicenter study that will use a test-negative, case-control design to assess the effectiveness of CAPVAXIVE in preventing hospitalized, confirmed community acquired pneumonia caused by *S. pneumoniae* serotypes contained in CAPVAXIVE among individuals ≥65 years of age.

A pilot study will be conducted to finalize selection of countries, hospital sites and data sources before study implementation.

Approximately 15,000 individuals are expected to be enrolled across the study sites. The Applicant is required to submit study progress reports no less frequently than every 180 days, which would allow for the monitoring of their actual enrollment against the protocol-specified enrollment targets.

Accelerated Approval Requirements

We remind you of your postmarketing requirement specified in your submissions of, February 14, 2024 and May 30, 2024.

2. To conduct an observational hybrid study using both primary and secondary data collection with a test-negative case-control design with the objective of assessing the effectiveness of CAPVAXIVE in preventing hospitalized, confirmed community acquired pneumonia (CAP, invasive and non-invasive) caused by *S. pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B in individuals ≥65 years of age. The protocol (V116-011-00) is entitled "A Test-Negative Case-Control Study to Evaluate the Effectiveness of V116 Against Pneumococcal Pneumonia in Older Adults."

- Serotype-Specific Urinary Antigen Detection (SSUAD) and Pneumococcal Antigen Detection (PAD) validation protocol submission: November 1, 2024
- SSUAD and PAD validation reports submission: May 30, 2025
- Final Protocol Submission: May 30, 2025
- Final Study Implementation Readiness Verification Submission: June 16, 2025
- Study Initiation: June 30, 2025
- Study Completion: June 29, 2029
- Final Study Report Submission: December 31, 2029