Summary Basis for Regulatory Action

Date:	June 8, 2021
From:	Christina Houck, Review Committee Chair, OVRR/DVRPA
BLA STN:	125731/0
Applicant:	Wyeth Pharmaceuticals LLC, a subsidiary of Pfizer, Inc.
Submission Receipt Date:	Rolling Submission: September 3, 2020 and October 8, 2020
Action Due Date:	June 8, 2021
Proper Name:	Pneumococcal 20-valent Conjugate Vaccine
Proprietary Name:	Prevnar 20
Indication:	Prevnar 20 is indicated for active immunization for the prevention of pneumonia and invasive disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F,14, 15B, 18C, 19A, 19F, 22F, 23F and 33F in adults 18 years of age and older.

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

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Director, Product Office

Discipline Reviews	Reviewer / Consultant
CMC • CMC Product (OVRR/DBPAP) • Facilities review (OCBQ/DMPQ) • Establishment Inspection Report (OCBQ/BMB) • QC, Test Methods, Product Quality (OCBQ/DBSQC)	Mustafa Akkoyunlu, MD, PhD James Erich Keller, PhD Lisa Parsons, PhD Wei Wang, PhD Malcolm Nasirah, PharmD, MS, BCGP Marie Anderson, PhD Ritu Agarwal, PhD Kouassi Ayikoe, PhD Anil Choudhary, PhD, MBA Hyesuk Kong, PhD Darya Melnyk, MSc
Clinical • Clinical (OVRR/DVRPA) • Postmarketing safety epidemiological review (OBE/DE) • BIMO	Tina Khoie Mongeau, MD, MPH Phillip Blanc, MD, MPH Malcolm Nasirah, PharmD, MS, BCGP
Statistical • Clinical data and Non-clinical data (OBE/DB)	Ruoxuan Xiang, PhD
Non-clinical/Pharmacology/Toxicology • Toxicology (OVRR/DVRPA)	LCDR Andrew O'Carroll, DVM
Labeling • Promotional (OCBQ/APLB) • PNR (OCBQ/APLB) • Container/Carton (OVRR/DVRPA)	Michael Brony Oluchi Elekwachi, PharmD, MPH Daphne Stewart
Other Review(s) not captured above categories, for example: • Accelerated Approval Protocol	Hector Izurieta, MD, MPH, PhD

Table of Contents

1. Introduction

On October 8, 2020, Wyeth Pharmaceuticals LLC, a subsidiary of Pfizer, Inc., submitted a biologics license application (BLA) for licensure of a 20-valent pneumococcal conjugate vaccine (PCV), completing their rolling BLA submission. The proposed proper name of the vaccine is Pneumococcal 20-valent Conjugate Vaccine and the proposed proprietary name is Prevnar 20. The proposed indications are active immunization of adults 18 years of age and older for the prevention of pneumonia and invasive disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F and 33F.

Under this BLA, Pfizer (the Applicant) is seeking traditional approval for the indication of invasive pneumococcal disease (IPD) caused by all 20 serotypes in Prevnar 20 (PCV20), as well as for the indication of pneumonia caused by the 13 pneumococcal serotypes included in Prevnar 13 (PCV13) (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F). The Applicant has also submitted an accelerated approval request for the pneumonia indication for the non-PCV13 serotypes in the vaccine (8, 10A, 11A, 12F, 15B, 22F and 33F).

PCV20 is composed of capsular polysaccharides derived from the 13 pneumococcal serotypes contained in PCV13 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) and from 7 additional pneumococcal serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) each individually conjugated to non-toxic diphtheria CRM_{197} protein. The vaccine dose is 0.5 mL and is supplied as a sterile liquid suspension for intramuscular injection in a pre-filled syringe.

2. Background

S. pneumoniae is a leading cause of disease and death among older adults in the United States (US). *S. pneumoniae* colonize the nasopharynx and can cause non-invasive disease (e.g., non-bacteremic pneumonia) as well as invasive disease (e.g., bacteremia and meningitis) in adults. IPD is defined by isolation of *S. pneumoniae* from a normally sterile site (i.e., blood, cerebrospinal, pleural or peritoneal fluid). The most common IPD syndromes in adults aged 50 years and older include invasive (bacteremic) pneumonia, bacteremia without a focus, and meningitis. Among patients hospitalized with community-acquired pneumonia, approximately 5%-10% will have pneumococcal bacteremia. Non-bacteremic pneumococcal pneumonia remains a more common disease manifestation, accounting for approximately 13%-34% of pneumonia hospitalizations among adults.

Currently, there are two pneumococcal vaccines available in the US for the prevention of pneumococcal disease in adults, Pneumovax® 23 (PPSV23) and PCV13. In 1983, the FDA approved PPSV23, the 23-valent pneumococcal polysaccharide vaccine, for use in persons ≥50 years of age and persons ≥2 years of age who are at increased risk of pneumococcal disease. Each 0.5 mL dose contains 25 µg of purified capsular polysaccharide from each of 23 pneumococcal serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N,

9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22, 23F, and 33F). PPSV23 has been the only pneumococcal vaccine licensed in the US for adults for the prevention of pneumococcal disease caused by the 7 new serotypes in PCV20; however, PPSV23 has not been demonstrated to be effective in the prevention of vaccine-serotype non-bacteremic pneumococcal pneumonia. These 7 serotypes are responsible for a substantial proportion of the current burden of invasive and noninvasive pneumococcal disease in adults globally. Non-bacteremic pneumococcal pneumonia continues to be a more common pneumococcal disease manifestation than IPD in adults. The Center for Biologics Evaluation and Research (CBER) therefore considers protection of adults ≥18 years of age from non-bacteremic pneumococcal pneumonia to be a meaningful therapeutic benefit over existing treatments.

Licensed in 2011, PCV13 was the first pneumococcal conjugate vaccine for use in adults in the US. It is a glycoconjugate vaccine consisting of purified capsular polysaccharide antigens of 13 *S. pneumoniae* serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) individually conjugated to non-toxic diphtheria CRM_{197} protein. PCV13 was approved, under Accelerated Approval regulations (21 CFR 601.41), for active immunization for the prevention of invasive disease and pneumonia caused by the 13 *S. pneumoniae* serotypes contained in the vaccine in persons ≥50 years of age based on a serological endpoint (opsonophagocytic activity (OPA) antibody titer). As a condition of accelerated approval, the Applicant completed a postmarketing study that confirmed and described the efficacy of PCV13 for the approved indications. In 2016, FDA approved an sBLA application to expand the usage of PCV13 for the approved indications to adults 18 through 49 years of age based on immunologic bridging studies.

The PCV20 Phase 3 clinical development program used an approach in which vaccine effectiveness against IPD caused by the 20 vaccine serotypes and against pneumonia caused by the 13 pneumococcal serotypes in PCV13 is inferred in adults ≥ 60 years of age from immunologic comparability (using an agreed-upon pre-specified non-inferiority criterion) to pneumococcal vaccines licensed in the US. PCV20 effectiveness in younger age groups (18 through 49 and 50 through 59) was supported by immunobridging to the established effectiveness in adults 60 through 64 years. The Center for Biologics Evaluation and Research (CBER) considered this approach acceptable for PCV20 because: 1) OPA reflects relevant *in vivo* mechanisms of protection against pneumococcal disease; 2) efficacy against pneumonia caused by the 13 serotypes had been confirmed in a clinical endpoint study (6115A1-3006; NCT00744263; and 3) PCV20 and PCV13 vaccines have nearly identical manufacturing processes for the 13 common serotypes. CBER did not consider immunogenicity data alone as sufficient to support a non-invasive disease indication (i.e., pneumonia) for the 7 new non-PCV13 serotypes included in PCV20, because antibody levels have not been found to be indicative of prevention of non-invasive pneumococcal disease.

Approval of PCV20 for the prevention of pneumonia in adults caused by the 7 new serotypes is based on an immunologic surrogate endpoint (OPA titer), that is reasonably likely to predict prevention of pneumococcal pneumonia caused by the 7 new vaccine serotypes in PCV20, as afforded by Accelerated Approval regulations (21 CFR 601.41). This regulation applies to biologics intended to treat or prevent serious or

life-threatening illnesses, and that provide meaningful therapeutic benefit to patients over existing treatments (21 CFR 601.40). Because pneumococcal pneumonia is a serious condition and PCV20 will provide meaningful therapeutic benefit to patients over existing treatments (i.e., PCV 13 and PPS23), the proposed indication meets the qualifying criteria for accelerated approval. As a condition of accelerated approval, the Applicant will conduct a post-approval real-world observational effectiveness study as a confirmatory study to verify and describe the clinical benefit for the prevention of pneumonia in adults caused by the 7 new serotypes in PCV20. CBER agreed that it would be reasonable to target adults ≥ 65 years of age for enrollment in the confirmatory study because of their higher rates of pneumococcal pneumonia. CBER considered that if PCV20 effectiveness against pneumonia due to the 7 new serotypes was confirmed in adults ≥ 65 years of age, it would be reasonable to infer vaccine effectiveness in adults 60 through 64 years of age. CBER also agreed that PCV20 vaccine effectiveness against pneumonia due to the 7 new serotypes in adults 18 through 49 years and adults 50 through 59 years of age could be bridged to the effectiveness in adults 60 through 64 years of age. The initial protocol synopsis for this study was received on April 5, 2019, and CBER's comments dated November 8, 2020, and July 20, 2020, were incorporated into a final draft protocol which was submitted to this BLA.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
1. Pre-IND meeting	2/7/2013
2. IND submission	10/6/2016
3. Fast Track designation granted	9/19/2017
4. Breakthrough Therapy designation granted	9/10/2018
5. Pre-BLA Written Response	3/16/2020
6. BLA 125731/0 Rolling Submission	9/3/2020 and 10/8/2020
7. BLA filed	12/3/2020
8. Priority Review granted	12/3/2020
9. Mid-Cycle communication	2/4/2021
10. Late-Cycle meeting	4/7/2021
11. Action Due Date	6/8/2021

3. Chemistry Manufacturing and Controls (CMC)

a. Product Quality

Product Composition

PCV20 is a sterile liquid suspension for intramuscular administration of *S. pneumoniae* capsular polysaccharide antigen subtypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F each conjugated to diphtheria Cross Reactive Material (CRM_{197}). Each 0.5 mL dose of PCV20 in a prefilled syringe is formulated to deliver 2.2 µg of each serotype-specific polysaccharide conjugate, except

for 6B, which is 4.4 µg/dose. The vaccine is formulated in (b) (4) succinate buffer containing (b) (4) sodium chloride (NaCl) and (b) (4) polysorbate 80, at (b) (4), and containing aluminum phosphate at (b) (4) aluminum as an adjuvant. Each 1-mL syringe contains a 0.5-mL dose of vaccine, supplied as a single-dose injection for parenteral administration, with no preservative.

(b) (4)

Manufacturing Overview

The polysaccharide serotypes from PCV13 are all manufactured in (b) (4), while the 7 new polysaccharide serotypes, CRM_{197}-(b) (4), and CRM_{197}-(b) (4) are manufactured in (b) (4). Conjugates using the 7 new serotypes are also manufactured in (b) (4), while conjugates of the original 13 serotypes are made in (b) (4). The final drug product is formulated in (b) (4).

Drug Substances

(b) (4)

(b) (4)

(b) (4)

Drug Product

Composition

The final drug product (DP) is composed of a mixture of the 20 conjugated drug substances (MBC serotypes mentioned previously) in a sterile liquid suspension in 1-mL glass, Luer-lock, prefilled syringes for intramuscular administration. Each 0.5 mL dose contains 2.2 µg of each serotype except 6B of which it contains 4.4 µg. The vaccine formulation contains the 20 MBCs in (b) (4) succinate/(b) (4) sodium chloride (NaCl) buffer, (b) (4) and aluminum phosphate (AlPO4) at (b) (4) mg/mL aluminum as an adjuvant with (b) (4) polysorbate 80 and no preservative.

Manufacturing

The manufacturing process for the PCV20 DP consists of the following steps:

- (b) (4)

- (b) (4)

Process Validation and Evaluation

Control of the PCV20 DP manufacturing process was demonstrated by maintaining process parameters within defined operating ranges specified in the manufacturing batch records. Process validation acceptance criteria included all critical process parameters and non-critical parameters and outputs based on early process and parameter evaluations and pre-process validation experience. Process performance assessments included (b) (4)

DP Specifications

PCV20 DP specifications for release and stability are included in Table 1 below. Up to (b) (4) different lots from different stages of development (i.e. clinical, phase 3) were evaluated to establish acceptance criteria specifications. Where relevant, the mean and standard deviation were calculated and tolerance interval levels set to (b) (4) standard deviations of the population at a 95% confidence interval (CI), then adjusted based on experience, robustness studies, stability studies, and historical knowledge of PCV13 DP. Some acceptance criteria values applied for the PCV13 serotypes used in PCV20 differ from those in the PCV13 vaccine. The (b) (4) was tightened from (b) (4) in PCV20 based on robustness studies. The acceptance criteria for (b) (4) protein was (b) (4) from (b) (4) This is acceptable as the Applicant found (b) (4)

Table 2: PCV20 Drug Product Specifications

Quality Attribute	**Analytical Procedure**	**Acceptance Criteria**
Aluminum concentration	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Total protein concentration	(b) (4)	(b) (4)
Appearance	visual inspection	homogeneous, white suspension (R,S)
Container Closure integrity[2]	(b) (4)	(b) (4)
Identity (Saccharide/CRM_{197})	(b) (4)	(b) (4)
(b) (4) PS80	(b) (4)	(b) (4)

Quality Attribute	Analytical Procedure	Acceptance Criteria
(b) (4)	(b) (4)	(b) (4)
Volume of injection	(b) (4)	(b) (4)
Endotoxin	(b) (4)	(b) (4)
Sterility	(b) (4)	No growth (R,S)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)

[1] R=used for release, S=used for stability
[2] Container closure integrity will be used *in lieu* of the sterility test during stability studies
[3] For the PCV13 vaccine, protein is , and is

Stability and Filling

The shelf life of PCV20 DP is 24 months when stored at 2-8 °C. This is based on stability data from primary stability lots stored in the horizontal position. Expiration dating is from the date of manufacture of the filled syringes, defined as the date filling is initiated, to (b) (4) less than the established expiration dating. Target DP batch sizes are (b) (4) . One stability study of 24 months has been performed on a (b) (4) production lot and two additional studies of 18 months on another (b) (4) lots were also performed. The longest stability study on a (b) (4) production lot at this time is 12 months. Although only twelve months of stability data are available for the (b) (4) batch, stability data to (b) (4) 24 months on smaller batches were within acceptance criteria and there is no indication that batch size has an impact on stability. The Applicant has committed to collecting (b) (4)-months of stability data on a minimum of one lot per year. The stability data provided in the submission support a dating period of 24 months from the date of manufacture when stored at 2-8 °C.

The PCV20 DP is made and filled on the same equipment used for the PCV13 DP and is presented in the same syringes and stoppers. The filled DP syringes are stored at 2-8 °C until ready to be shipped from (b) (4) , where the syringes are packaged and labeled. (See 3e Container/Closure System.)

Comparability Protocols

Comparability protocols for preparation, qualification, storage, and shipping of future WCBs for all the PCV13 serotypes that currently have MCBs: 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F, and for CRM_{197} were submitted. Qualification involves testing for (b) (4) . The Applicant plans to report new WCB lots for all serotypes and CRM_{197} in annual reports to the BLA. This was found acceptable.

b. Testing Specifications

The analytical methods and their validations and/or qualifications reviewed for the PCV20 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. Inspection histories and activities for facilities involved in the manufacture of PCV20 vaccine are summarized in Table 2 below.

Table 3: Manufacturing Facilities Table for Pneumococcal 20-valent Conjugate Vaccine

Name/Address	FEI Number	DUNS Number	Waiver	Justification/ Results
Wyeth (b) (4) *Drug Substance Intermediates Manufacturing and Testing (Prevnar 13 serotypes, including pneumococcal polysaccharide serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F (13vPnC))*	(b) (4)	(b) (4)	Waived	ORA (b) (4) VAI
Wyeth (b) (4) *Drug Substance Intermediates Manufacturing and Testing* *(7 additional pneumococcal polysaccharide Serotypes 8, 10A, 11A, 12F, 15B, 22F, and 33F*	(b) (4)	(b) (4)	Waived	Team Biologics (b) (4) VAI

Name/Address	FEI Number	DUNS Number	Waiver	Justification/ Results
(7vPnC), and diphtheria CRM_{197} protein). *Drug Substance Manufacturing and Testing* *(pneumococcal polysaccharide-CRM_{197} conjugate Serotypes 8, 10A, 11A, 12F, 15B, 22F, and 33F)*				
Pfizer (b) (4) *Drug Substance Manufacturing (pneumococcal polysaccharide-CRM_{197} conjugate Serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F)* *Final Bulk Product Formulation and Syringe Filling, Primary packaging and release testing of drug product in syringes.*	(b) (4)	(b) (4)	Waived	Team Biologics (b) (4) VAI

CBER waived the pre-license inspections based on the following surveillance inspections performed by Team Biologics and Office of Regulatory Affairs of the facilities involved with the manufacture of pneumococcal vaccine:

Office of Regulatory Affairs performed a surveillance inspection of Wyeth (b) (4) . All 483 issues were resolved and the inspection was classified as voluntary action indicated (VAI).

Team Biologics performed a surveillance inspection of Wyeth (b) (4) . All 483 issues were resolved and the inspection was classified as VAI.

Team Biologics performed a surveillance inspection of Pfizer (b) (4) All 483 issues were resolved and the inspection was classified as VAI.

e. Container/Closure System

The drug product (0.5 mL dose with an overfill of (b) (4) mL) is filled into 1-mL single-dose (b) (4) borosilicate glass syringes (b) (4) Plastic Rigid Tip Cap (PRTC, (b) (4) syringes) or (b) (4) syringes) tip cap assembly that includes a Luer-lock adapter, a rigid cap, and a tip cap. The product contact tip cap is composed of gray (b) (4) elastomer (b) (4) rubber). The filled syringe is sealed with a (b) (4) plunger stopper composed of gray (b) (4) elastomer (b) (4) rubber). The syringe barrel and plunger stopper are (b) (4). A non-product contact plunger rod and finger grip are assembled to the syringe device system. The Applicant conducted container closure integrity testing at the (b) (4) employing the (b) (4) method; all acceptance criteria were met.

f. Environmental Assessment

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

4. Nonclinical Pharmacology/Toxicology

PCV20, similar products and the PCV20 vehicle were evaluated in six repeat-dose toxicity studies, one developmental and reproductive toxicity (DART) study and one single-dose subcutaneous local tolerance study to support the safety and risk assessment in (b) (4) rabbits. There were no toxicological findings that would preclude the use of this vaccine in its intended human population. However, histologic evidence of inflammation with degeneration/necrosis of cardiomyocytes was observed at low incidence and initially deemed test article-related by the study pathologist. There were no clinical manifestations observed for this finding in the study rabbits and the relevance and translatability to human subjects should be considered inconclusive at this time.

In the repeat-dose toxicity studies, rabbits received one of the following: saline control, vehicle control, a (b) (4)-valent version of the vaccine, the intended clinical dose of PCV20, or a high dose of PCV20 (2x the clinical dose). Aside from the aforementioned histologic finding, there were no treatment-related findings of clinical concern. Treatment-related findings included slightly increased incidence of irritation at injection sites, masses at injection sites, elevations in the acute phase reactants fibrinogen and C-reactive protein, increased germinal center formation in the spleen and injection site-draining lymph nodes, and injection site myofiber chronic-active inflammation with degeneration/necrosis. All of these findings were considered either partially or fully reversible and are considered anticipated sequelae of the intended immune response rather than as a sign of frank toxicity.

In the DART study, virgin rabbit does received saline control or 46.2 µg of PCV20 (4.4 µg per serotype except for 8.8 µg serotype 6B, the intended clinical dose) twice prior to mating and twice while pregnant. One subset of does from both groups had terminal caesarean sections on gestation day 29 (near term) to assess uterine effects and fetal development while another subset proceeded to parturition with both the does and F1 kits followed until 35 days postpartum. There was no treatment-related mortality or any treatment-related effects on female fertility and mating performance, fetal development, parturition or postnatal development up until 35 days postpartum. No treatment-related malformations or variations were observed in fetuses or kits in this study. Immunology testing in this study demonstrated evidence of passive transfer of antibodies from vaccinated does to fetuses and kits.

The single-dose subcutaneous local tolerance study, while limited in design and scope, demonstrated that PCV20 was well tolerated when administered subcutaneously and thus, would not pose any added risk should PCV20 be inadvertently administered through this route.

Adequate data were presented to demonstrate safety and tolerability of PCV20 when administered with the adjuvant aluminum phosphate IM. There was no clinically-relevant evidence of maternal toxicity (to include female fertility) or teratology when administered to pregnant rabbit does. Evidence of systemic inflammation and positive titers on serology adequately demonstrate the immunomodulatory effect of the vaccine. No toxicological findings were found which would preclude the use of this vaccine in its intended human population at doses up to 4.4 µg per serotype (and 8.8 µg for serotype 6B) up to 5 times intramuscularly.

5. Clinical Pharmacology

Mechanism of Action

PCV20 elicits an opsonophagocytic antibody response.

Nonclinical and clinical data support opsonophagocytic activity, as measured by a microcolony (mc) OPA assay. 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 pneumococcal disease. mcOPA titers are expressed as the reciprocal of the highest serum dilution resulting in 50% reduction in the number of bacterial colony-forming units, when compared with the control without test serum.

No specific threshold of OPA titer has been identified that correlates with protection against IPD or pneumonia in adults.

6. Clinical/Statistical

a. Clinical Program

The clinical development program for PCV20 included six clinical trials evaluating PCV20 in 7048 immunocompetent adults ≥18 years of age conducted in the U.S. and Sweden. The clinical studies consisted of two Phase 1 studies (B7471001, B7471005), one Phase 2 study (B747002), and three Phase 3 studies (B7471007, B7471008 and B7471006). The three Phase 3 studies were the primary safety and immunogenicity trials. The Phase 3 clinical program used an approach in which vaccine effectiveness against IPD caused by the 20 vaccine serotypes and against pneumonia caused by the 13 pneumococcal serotypes in PCV13 was inferred from immunologic comparability (using an agreed-upon pre-specified non-inferiority criterion) to a U.S. licensed pneumococcal vaccine. Detailed summaries of the Phase 3 clinical study program and supporting studies are listed below.

Phase 3 Studies

Phase 3 Non-inferiority Immunogenicity Study (B7471007)

The effectiveness of PCV20 was established in persons 60 years of age and older in study B7471007 by demonstrating immunologic noninferiority of the serotype-specific OPA antibody responses induced by PCV20 compared to the corresponding serotypes-specific OPA antibody responses induced by a licensed pneumococcal conjugate vaccine.

The effectiveness of PCV20 in younger adults 18-49 years of age and 50-59 years of age was demonstrated in the same study (B7471007) by immunobridging to the established effectiveness in the 60-64-year-old adult age group in Cohort 1.

Study B7471007 was a randomized, double-blind, multicenter study conducted in the US and Sweden. A total of 3,880 pneumococcal vaccine-naïve adults ≥18 years of age were enrolled into 1 of 3 age-based cohorts. Cohort 1 subjects (≥60 years of age) were randomized 1:1 to receive either PCV20 followed by saline placebo approximately one month later (PCV20/saline) or PCV13 followed by PPSV23 approximately one month later (PCV13/PPSV23). Cohort 2 subjects (50 through 59 years) and Cohort 3 subjects (18 through 49 years) were randomized 3:1 to receive PCV20 or PCV13. All subjects enrolled in Sweden were ≥65 years of age. The composition of the study populations was 58%-69% female, 81%-90% White, 6%-14% Black and <6% from other racial groups across all cohorts; 4%-11% were Hispanic/Latino; and 11%-20% were current smokers.

The primary immunogenicity objective was to assess noninferiority of immune responses elicited by PCV20 to those elicited by PCV13 for each of the 13 matched serotypes and by PPSV23 for each of the 7 additional serotypes, in subjects ≥60 years of age. PCV20 met the primary immunogenicity objective for the 13 matched vaccine serotypes. One month after PCV20 or PCV13, the immune responses to all 13-matched

vaccine serotypes induced by PCV20 were noninferior to those induced by PCV13, as demonstrated by the lower bounds of the 2-sided 95% CIs for the primary analysis of model-based OPA geometric mean (titer) ratios (GMRs) (PCV20 relative to PCV13) >0.5. The observed OPA GMRs for the 13 matched serotypes were between 0.76 and 1.00.

PCV20 also met the primary immunogenicity objective for 6 of the 7 additional vaccine serotypes. One month after PCV20 or PPSV23, the immune responses to 6 of the 7 additional vaccine serotypes induced by PCV20 were noninferior to those induced by PPSV23, as demonstrated by the lower bounds of the 2-sided 95% CIs for the primary analysis of model-based OPA GMRs (PCV20 relative to PPSV23) >0.5. The model-based GMR (2-sided 95% CI) for serotype 8 was 0.55 (0.49, 0.62), narrowly missing the statistical NI criterion. In supportive analyses of secondary endpoints, a substantial proportion of subjects in Cohort 1 achieved a ≥4-fold increase in anti-serotype 8 OPA antibody titers (77.8%). Altogether, the available data support the ability of PCV20 to elicit functional antibodies against serotype 8 that will likely contribute to protection against IPD and pneumococcal pneumonia.

The secondary immunogenicity objectives aimed to bridge the immune responses to PCV20 in younger subjects (Cohorts 2 and 3) to those in subjects 60 through 64 years of age (Cohort 1 subset). PCV20 met the secondary objectives for all 20 vaccine serotypes based on comparison of the immune responses in Cohort 2 to those in the Cohort 1 subset, and comparison of the immune responses in subjects in Cohort 3 to those in the Cohort 1 subset. One month after PCV20, the immune responses to all 20 vaccine serotypes in Cohort 2 were noninferior to those in the Cohort 1 subset of participants 60 through 64 years of age, as demonstrated by the lower bounds of the 2-sided 95% CIs for the primary analysis of model-based OPA GMRs (PCV20 in Cohort 2 relative to PCV20 in Cohort 1 participants 60-64 years of age) >0.5.

Phase 3 Study in Adults Previously Immunized with PCV13 and/or PPSV23 (B7471006)

Study B7471006 was a randomized, open-label, multicenter descriptive safety and immunogenicity study of PCV20 conducted in the United States and Sweden in 875 adults ≥65 years of age who have been previously vaccinated with PPSV23 (Cohort A), PCV13 (Cohort B), or PCV13 followed by PPSV23 (Cohort C). Cohort A and B participants were randomized 2:1 to receivePCV20 or a licensed pneumococcal vaccine that they had not previously received (PCV13 in Cohort A and PPSV23 in Cohort B) that served as active controls for safety assessments; all Cohort 3 participants received PCV20 . The composition of the study populations was 44%-48% males, 90%-94% White, 3%-7% Black, and 0.8%-3.3% were among other racial groups (Asian, American Indian or Alaskan Native, Native Hawaiian or other Pacific Islander, Multiracial or not reported). In Cohort A, 35.5% of the participants were enrolled in Sweden.

The primary immunogenicity objective was to describe the immune responses to PCV20 in adults previously vaccinated with PPSV23, previously vaccinated with PCV13, or previously vaccinated with both PCV13 and PPSV23. OPA GMTs in participants who

received PPSV23 1 to 5 years prior to Prevnar 20 were diminished compared to OPA GMTs in participants who received Prevnar 13 at least 6 months previously and compared to OPA GMTs in participants who received Prevnar 13 followed by PPSV23, with the last PPSV23 dose given at least 1 year prior to Prevnar 20.

The safety and tolerability profile of PCV20 was generally similar in participants with different prior pneumococcal vaccine history and was generally similar to PCV13 and PPSV23 control groups.

Phase 3 Lot Consistency Study (B7471008)

Study B7471008 was a randomized, double-blind, multicenter study with a 4-arm parallel design conducted in the US to provide clinical data supporting manufacturing consistency. A total of ~1,610 adults 18 through 49 years of age with no history of pneumococcal vaccination were planned to be enrolled and randomized (via site-based randomization) into 1 of 4 groups in a 2:2:2:1 ratio to receive one of three manufacturing scale lots of PCV20 or PCV13. The PCV13 group was a control for safety only, but sera were assayed to maintain blinding and for descriptive purposes. Adults 18-49 years of age with no history of pneumococcal vaccination were selected as the study population because they have lower variability in immune response than potentially previously vaccinated older populations, thus facilitating interpretation of immunogenicity results for lot consistency.

The primary immunogenicity objective was to demonstrate that the immune responses to 20 serotypes induced by PCV20 were equivalent across three manufacturing scale lots. The lot-to-lot consistency was to be evaluated by each primary immunogenicity endpoint, serotype-specific OPA titer 1 month after vaccination, using a 2-fold equivalence margin for each between-lot comparison of OPA titers. Lot consistency was demonstrated based on a 2-fold equivalence margin comparing the OPA GMTs between each pair of PCV20 lots for each serotype. The 2-sided 95% CIs for the model-based estimate of serotype-specific OPA GMRs 1 month after vaccination for each pair of lot comparisons (Lot 1/Lot 2, Lot 1/Lot 3, and Lot 2/Lot 3) are contained in the pre-specified interval (0.5, 2.0) for each of the 20 serotypes.

The secondary immunogenicity objective was to describe the immune responses to PCV20 in terms of 1) Fold rise in serotype-specific OPA titers from before to 1 month after vaccination; 2) ≥4-Fold rise in serotype-specific OPA titers from before to 1 month after vaccination; and 3) Serotype-specific OPA titers ≥ LLOQ 1 month after vaccination. The secondary endpoints were met with generally similar outcomes across all three lots of PCV20 for each of the 20 serotypes 1 month after vaccination.

The Applicant satisfactorily demonstrated lot-to-lot manufacturing consistency based on comparisons of OPA GMTs of three different clinical lots of PCV20 in study B7471008. The safety profile of PCV20 among participants who received each manufacturing scale lot was comparable to the safety profile of U.S.-licensed Prevnar 13 (the active control in this study), and there were no important differences observed in safety outcomes among the three different manufacturing scale lots.

Phase 1 and 2 Studies

Phase 2 Study (B7471002)

Study B7471002 was a descriptive Phase 2, multicenter, randomized (1:1), active controlled, double-blind trial to describe the safety and immunogenicity (serotype-specific OPA antibody titers) of PCV20 in approximately 400 adults 60-64 years of age in the United States with no prior pneumococcal vaccination history. The treatment group received a single dose of PCV20 followed 1 month later by saline (placebo); the control group received a single dose of PCV13 followed 1 month later by a dose of PPSV23. PCV13 served as a control for safety and immunogenicity of the 13 original vaccine serotypes. PPSV23 served as a control for immunogenicity of the 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F).

Of the 222 subjects enrolled and randomized to the control group, 222 received PCV13 on study day 1 and 214 received PPSV23 on study days 28-35. For the 13 original vaccine-type serotypes, OPA GMTs among PCV20 recipients were generally similar to or lower than those of PCV13 recipients. Based on data submitted to CBER on July 12, 2018, in support of Breakthrough Therapy Designation, the lower limit of the 95% CI for the OPA GMT ratios (PCV20/PCV13) was >0.5 for 10 serotypes. The lower limit of the 95% CI for the OPA GMR was 0.47, 0.48, and 0.43 for serotypes 1, 5 and 19F, respectively. For the 7 new serotypes, OPA GMTs were generally higher following PCV20 compared to PPSV23, except for serotype 8.

Results from study B7471002 provided safety and immunogenicity data supporting Phase 3 clinical development of PCV20. The data from this study also supported the Applicant's request at the time for Breakthrough Therapy Designation.

Phase 1 Studies (B7471005 and B7471001)

Study B7471005 was a randomized (1:1:1), controlled, double-blind, 3-arm multicenter study that evaluated the safety and immunogenicity of PCV20 in adults. A total of 104 healthy pneumococcal vaccine naïve Japanese adults 18-49 years of age residing in the United States were enrolled and randomized equally to receive PCV20, investigational complementary 7-valent pneumococcal conjugate vaccine (c7vPnC) or PCV13 vaccine. This trial provided data to support clinical development of PCV20 in Japan. Adverse events were coded using MedDRA version 21.1.

Before vaccination, OPA GMTs for all 20 serotypes were similar among the 3 vaccine groups. At 1 month after vaccination, increases in OPA GMTs were observed for all 20 serotypes in the PCV20 group. Most subjects in the PCV20 group achieved a ≥4-fold rise in OPA titers for all 20 serotypes from before to 1 month after vaccination. The results of this study supported continued development of PCV20 for use in adults.

Study B7471001 was a first-in-human, randomized (1:1), active-controlled, observer-blinded trial that evaluated the safety and immunogenicity of PCV20 in a total of 66

healthy pneumococcal vaccine naïve adults 18-49 years of age. The trial was conducted at the Pfizer Clinical Research Unit (PCRU) in New Haven, Connecticut. Subjects meeting eligibility criteria were admitted to the PCRU and randomized (1:1) to receive PCV20 or a US-licensed tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine, adsorbed (Tdap manufactured by Sanofi Pasteur (Adacel)) as the active control.

The immunogenicity results from this Phase 1 descriptive study demonstrated that PCV20 is immunogenic in healthy adults 18-49 years of age. Pre-vaccination titers were generally low, although baseline titers to serotypes 10A, 11A, 22F, and 33F were numerically higher. A numerical increase in OPA GMTs from before to 1 month after vaccination was observed for each of the 20 vaccine serotypes. The OPA GMTs were essentially unchanged after vaccination in the Tdap recipients.

The safety and immunogenicity results from this study supported initiation of Phase 2 study B7471002 in adults 60-64 years of age. This Phase 2 study included a program-level external data monitoring committee that would remain in place throughout the PCV20 clinical development program to conduct routine, periodic safety reviews of the Phase 2 and Phase 3 studies in the clinical program.

Postmarketing

As a condition of accelerated approval, the Applicant agrees to conduct a post-approval confirmatory study to verify and describe the clinical benefit of PCV20 in adults ≥65 years of age. To fulfill the postmarketing requirement, the Applicant submitted a protocol for study B7471015 (STN 125731/0.8); the proposed Phase 4 post-approval study is a multicenter real-world evidence (RWE) investigation to evaluate the effectiveness of PCV20 against radiologically-confirmed community-acquired pneumonia (RAD+CAP) caused by the 7 additional serotypes using a test-negative case control design to be conducted at investigator hospital sites in the United States. The primary objective is to determine vaccine effectiveness (VE) of PCV20 against RAD+CAP caused by the 7 additional serotypes contained in PCV20 beyond the licensed 13-valent pneumococcal conjugate vaccine (PCV13; serotypes 8, 10A, 11A, 12F, 15B, 22F, and 33F) plus 15C among adults ≥65 years of age. Approximately 12,500 adults ≥65 years of age are expected to be enrolled at approximately 10–20 sites. Further discussions between CBER and the Applicant will be needed post-approval to finalize the protocol.

Postmarketing studies that the Applicant is required to conduct under PREA following licensure include studies B7471011, B7471013 and B7471014. The protocols for each of these studies were submitted in 2020. They have now been initiated and are ongoing. Study B7471011 will evaluate the safety and effectiveness of a 4-dose series of PCV20 administered in the United States at 2, 4, 6 and 12 months of age in infants 6 weeks through 12 months of age. Study B747103 will evaluate the safety of 2, 4, 6, and 12-month schedules of PCV20 in infants in the United States, Europe, and Canada. Study B7471014 will evaluate the safety and effectiveness of PCV20 in children and adolescents 15 months through 17 years of age.

A safety and immunogenicity trial of PCV20 co-administered with seasonal inactivated influenza vaccine in adults ≥65 years of age is currently ongoing. (b) (4)

Clinical Serology Assay

Microcolony Opsonophagocytic Antibody Assay
Opsonophagocytic activity, measured via a microcolony OPA (mcOPA) assay, was selected as a surrogate endpoint for demonstrating the effectiveness of PCV20 in adults ≥18 years of age. The mcOPA assay for *S. pneumoniae* is designed to assess the ability of functional antibodies obtained from heat-inactivated human serum to bind to serotype-specific pneumococcal bacteria in the presence of a functional complement source thereby facilitating bacterial engulfment and death by phagocytic cells. This assay was used to measure OPA response in all Phase 3 studies in the PCV20 clinical program.

This assay uses bacterial microcolonies for the enumeration of viable bacterial cells. An OPA titer is defined as the titer that results in killing 50% of the bacteria and is calculated by interpolation between the two data points that are immediately below and above the 50% level.

The mcOPA assay was validated for the following parameters: linearity, precision, lower limit of quantitation, limit of detection, and specificity. Overall, the mcOPA was determined to be validated appropriately for the intended purpose.

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

Bioresearch Monitoring (BIMO) inspections were issued for three clinical study sites that participated in the conduct of study Protocol B7471007. The inspections did not reveal substantive issues that impact the data submitted in this 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 Pediatric Study Plan was presented to FDA's Pediatric Review Committee (PeRC) on May 4, 2021. 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. During the review cycle, the Applicant revised the pediatric timelines, submitted in the Pediatric Study Plan, along with a justification for the changes. PeRC agreed to these revisions.

Safety and effectiveness of PCV20 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 zero through 16 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 zero to <6 weeks of age for the invasive pneumococcal disease indication because PCV20 does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and PCV20 is not likely to be used by a substantial number of pediatric patients in this age group (section 505B(a)(4)(B)(iii) of the Act).

The Applicant is requesting a deferral of pediatric studies in persons 6 weeks through 16 years of age to support the invasive pneumococcal disease indication on the basis that PCV20 is ready for approval for use in adults and the pediatric studies have not been completed (505B(a)(3)(A)(i) of the Act).

d. Other Special Populations

Not Applicable.

7. Safety and Pharmacovigilance

The safety profile for PCV20 includes a total of 7,048 immunocompetent adults ≥18 years of age evaluated in six PCV20 pre-licensure trials. A total of 3,928 subjects and 2,247 subjects received PCV20 or active control, respectively, and provided post-vaccination safety data from 5 randomized, double-blinded, active controlled clinical trials conducted in immunocompetent pneumococcal vaccine naïve adults ≥18 years of age in the United States and Sweden (172 subjects ≥65 years of age were randomized/enrolled in Sweden). Additional descriptive data were available from a sixth open-label study in adults ≥65 years of age in the United States and Sweden previously immunized with a pneumococcal vaccine prior to enrollment (624 PCV20 recipients and 245 active control recipients in B7471006).

The methods for safety data collection and analysis were the same for all the trials. Specific reactions and events were reported by subjects by using an electronic diary. Safety monitoring for subjects included:

- observation for 30 minutes after vaccination for immediate severe reaction;
- local reactions (redness, swelling, and pain at the injection site) occurring within 10 days after vaccination;
- systemic events (fever, headache, fatigue, muscle pain, and joint pain) occurring within 7 days after vaccination;
- use of antipyretic or pain medications within 7 days after vaccination;
- Adverse events (AEs) occurring within 1 month after vaccination;

- Serious adverse events (SAEs) occurring within 6 months after vaccination;
- Newly diagnosed chronic medical conditions occurring within 6 months after vaccination.

MedDRA version 22.1 coding dictionary was applied in studies B7471008 and B7471006.

Safety Results

Post-vaccination safety data were collected from 6 randomized studies in which 7,048 immunocompetent adults ≥18 years of age were immunized with either PCV20 (N=4,552) or an active control (N=2,496). This included an open-label safety assessment among 869 (624 PCV20 recipients and 249 control recipients) adults ≥65 years of age previously immunized with at least one dose of a pneumococcal vaccine prior to enrollment. No safety concerns were identified when a single dose of PCV20 was administered to pneumococcal-vaccine-naïve or pneumococcal-vaccine-experienced adults ≥18 years of age.

The most frequently reported adverse reactions were injection site pain, muscle pain, fatigue, headache, and joint pain. Adverse reaction rates were highest among subjects in the oldest age cohort and decreased with decreasing age. Most reactions were mild or moderate in severity. There were no serious adverse events (SAEs) that were related to the study vaccine.

Withdrawals due to AEs were reported for 20 subjects in Cohort 1 of study B7471007, and no withdrawals were reported in studies B7471008 or B7471006. Two unrelated deaths were reported involving a 60-year-old male in Cohort 1 of study B7471007 and a 37-year-old female in study B7471001.

The available safety data does not substantiate a need for safety-related postmarketing studies.

Pharmacovigilance Plan

The Applicant submitted a Pharmacovigilance Plan (PVP) for PCV20, which was found to be acceptable. The Applicant agrees to carefully monitor for any unanticipated risks in surveillance systems and postmarketing adverse reaction reports (i.e., routine pharmacovigilance).

8. Labeling

The proposed proprietary name, PREVNAR 20, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on January 5, 2021 and was found acceptable. CBER communicated the acceptability of the proprietary name to the Applicant on January 6, 2021.

The APLB reviewed the proposed Prescribing Information on April 6, 2021 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 3, 2020, 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 approval of PCV20 for the labeled indication and usage.

b. Benefit/Risk Assessment

Considering the data submitted to support the safety and efficacy of PCV20 that have been presented and discussed in this document, the Review Committee is in agreement that the risk/benefit balance for PCV20 is favorable and supports approval for use in individuals 18 years of age and older for the prevention of vaccine-type IPD and vaccine-type pneumococcal pneumonia.

c. Recommendation for Postmarketing Activities

The Applicant has committed to conduct the following postmarketing requirements (PMR), which are specified in the approval letter for this application.

1. Please commit to a deferred pediatric study (B7471011) under PREA to evaluate the safety and effectiveness (immunogenicity) of the 2, 4, 6, and 12-month schedule of PCV20 in United States (US) infants 6 weeks through 12 months of age.

   Final Protocol Submission: May 8, 2020
   Study Completion: August 31, 2022
   Final Report Submission: December 31, 2022

2. Please commit to a deferred pediatric study (B7471013) under PREA to evaluate the safety of the 2, 4, 6, and 12-month schedule of PCV20 in US, European, and Canadian infants 6 weeks through 12 months of age.

   Final Protocol Submission: March 23, 2020
   Study Completion: August 31, 2022
   Final Report Submission: December 31, 2022

3. Please commit to a deferred pediatric study (B7471014) under PREA to evaluate the safety and effectiveness (immunogenicity) of PCV20 in US children and adolescents 15 months through 17 years of age.

   Final Protocol Submission: September 11, 2020
   Study Completion: December 31, 2021
   Final Report Submission: December 31, 2022

Accelerated Approval PMR:

Final Protocol Submission: August 31, 2020
Study Completion: May 31, 2027
Final Report Submission: November 30, 2027