

**CBER CMC BLA Review Memorandum**

**BLA STN 125731**

**20-valent Pneumococcal Conjugate Vaccine (PF-06482077; 20vPnC)  
Prenar 20**

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Review**

1. **BLA#:** STN 125731

2. **APPLICANT NAME AND LICENSE NUMBER**

Wyeth Pharmaceuticals LLC, a subsidiary of Pfizer Inc

3. **PRODUCT NAME/PRODUCT TYPE**

PREVNAR 20

20-valent Pneumococcal Conjugate Vaccine [20vPnC]

4. **GENERAL DESCRIPTION OF THE FINAL PRODUCT**

- a. Vaccine
- b. Sterile, preservative free solution for injection supplied in unit dose vials.
- c. The Drug Product active ingredients are *Streptococcus pneumoniae* capsular polysaccharide subtypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F each individually conjugated to diphtheria toxin CRM<sub>197</sub>. The target active ingredient concentrations are 2.2 µg of each polysaccharide except 6B which is 4.4 µg and approximately 51 µg of CRM<sub>197</sub> per 0.5 mL dose.
- d. Intramuscular injection
- e. In adults 18 years of age and older

5. **MAJOR MILESTONES**

- Fast tract Designation was granted 19 September 2017 and Breakthrough Therapy Designation on 10 September 2018. FDA approved the proposal for rolling submission of this BLA on 16 March 2020.
- Part 1 of the rolling BLA was submitted 03 September 2020. Part 2 was submitted 08 October 2020.
- A request for reference product designation was received 08 October 2020. CBER's reference product determination board met on 06 April 2021 and concurred with the CMC reviewer's recommendation to grant the designation. Upon approval, the product will be designated as a reference product and the associated exclusivity periods will be based upon the date of first approval.
- The PDUFA Action Due Date is 08 June 2021.

## 6. CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Lisa Parsons, OVRP/DBPAP/LBP	1.3.5.3 Exclusivity 3.2.S, 3.2.P Pneumococcal polysaccharide drug substances and conjugated drug product
James E. Keller, OVRP/DBPAP/LRSP	3.2.S.2 Drug Substance Manufacture (for CRM <sub>197</sub> -CY and CRM <sub>197</sub> -DM)
Mustafa Akkoyunlu, OVRP/DBPAP/LBP	4.2.1 Pharmacology 4.2.3 Toxicology 5.3.1 Reports of Biopharmaceutical Studies 5.3.3 Reports of Human Pharmacokinetic (PK) Studies 5.3.5 Reports of Efficacy and Safety Studies

## 7. INTER-CENTER CONSULTS REQUESTED

No inter-center consults were requested.

## 8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
09/03/2020	STN 125731/0	Rolling submission #1 clinical content
10/08/2020	STN 125731 /0.1	Rolling submission #2 CMC content
11/02/2020	STN 125731/0.3	CMC Stability data/
11/17/2020	STN 125731/0.4	CMC Stability data
12/16/2020	STN 125731/0.5	Response to IR-1 (12/07/20) CMC/Serology/CMC Q2 by LP in 3.2.R
01/22/2021	STN125731/0.9	Response to IR-2 (01/19/21) Serology
02/02/2021	STN 125731/0.12	Response to IR-2 (01/19/21) CMC: MCB QQR1/(b) (4) Valid QQR2/Cult (b) (4) QQR3/ leaking FCs QQR4/ reviewed by LP in 3.2.S.2.3, 3.2.S.2.4, 3.2.S.2.5
02/09/2021	STN 125731/0.14	Response to IR-3 (01/26/21) Exclusivity/ reviewed by LP in Exclusivity Response to Biostats CMC: Comparability/ CMC reviewed by LP in 3.2.P.2.3
02/10/2021	STN 125731/0.15	Response to IR-4 (02/03/21) Serology; reviewed by MA in Serology

Date Received	Submission	Comments/ Status
02/16/2021	STN 125731/0.16	Response to IR-5 (02/16/21) Serology: (b) (4); reviewed by MA in Serology
02/25/2021	STN 125731/0.18	Response to IR-6 (02/25/21) CMC: CRM <sub>197</sub> / reviewed by EK in Sections 3.2.S.2.2 and 3.2.S.2.3
03/16/2021	STN 125731/0.23	Response to IR-7 (03/02/21) CMC: QQR on E/L, validation, MBR by LP in 3.2.S.2.5 & 3.2.S.4.3 /CRM <sub>197</sub> by EK
04/15/2021	STN 125731/0.28	Response to IR-8 (4/2/21) CMC: (b) (4) stability/ reviewed by EK in 3.2.S.7
04/21/2021	STN 125731/0.31	Response to IR-9 (4/08/21) Serology to support P4 study -valid (b) (4), UAD-(b) (4) assays; reviewed by MA in Serology

## 9. REFERENCED REGULATORY SUBMISSIONS

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
IND 17039	Pfizer Inc.	20vPnC	NO	No review required. This is listed for information only. Pertinent information is provided in the BLA.
BLA 125324	Pfizer Inc.	Prevnar 13	NO	No review required information pertinent to the 13vPnC serotypes is provided in the BLA
Type III DMF (b) (4)	(b) (4)	(b) (4) glass syringe with plastic rigid tip cap  (b) (4) Luer lock connection (b) (4) plunger rod	YES	No review required; information pertinent to container closure is provided in the BLA

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
Type III DMF (b) (4)	(b) (4)	(b) (4) 1 mL glass syringe with (b) (4) rigid cap Luer lock connection	YES	No DMF review required, information pertinent to container closure is provided in the BLA
Type III STN (b) (4)	(b) (4)	Syringe tip cap composed of gray (b) (4) elastomer  1-3 mL plunger stopper composed of gray (b) (4) elastomer	YES	No review required; information pertinent to container closure is provided in the BLA

## 10. REVIEWER SUMMARY AND RECOMMENDATION

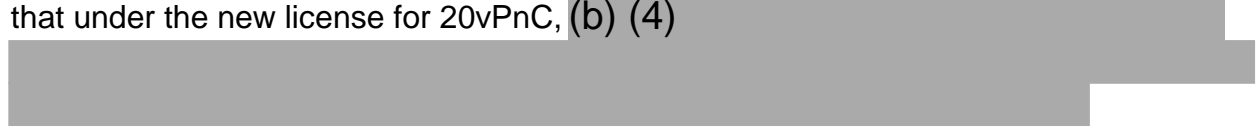
### A. EXECUTIVE SUMMARY

Pfizer is seeking licensure of a 20-valent pneumococcal conjugate vaccine (20vPnC) composed of twenty different *Streptococcus pneumoniae* polysaccharides (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F) conjugated to diphtheria Cross Reactive Material (CRM<sub>197</sub>). Thirteen of these serotypes (1, 3, 4, 5, 6A, 6B, 7F, 19A, 9V, 14, 18C, 19F, and 23F) are also included in Pfizer's licensed pneumococcal polysaccharide conjugate vaccine, Prevnar13® (13vPnC). The proposed indication for 20vPnC is active immunization for the prevention of invasive pneumococcal disease (IPD) and pneumonia caused by the twenty serotypes in adults 18 years of age and older.


CRM<sub>197</sub> and new serotypes 8, 10A, 11A, 12F, 15B, 22F, and 33F are manufactured, tested, and conjugated at Wyeth in (b) (4) then shipped to Pfizer in (b) (4). The 13vPnC serotypes are manufactured and tested at Wyeth in (b) (4) prior to shipment to (b) (4) where they are conjugated to CRM<sub>197</sub>. 20vPnC vaccine formulation, syringe filling, primary packaging, and testing is completed at (b) (4).

CRM<sub>197</sub> may be manufactured with either casamino acid-yeast extract based medium (CRM<sub>197</sub>-CY) or defined medium (CRM<sub>197</sub>-DM). Both processes are currently approved for 13vPnC. For manufacture of 20vPnC, no changes have been made to the licensed


manufacturing processes for CRM<sub>197</sub>-CY and CRM<sub>197</sub>-DM. The sponsor has proposed that under the new license for 20vPnC, (b) (4)




There have been no significant changes to the approved processes for the production of the 13vPnC serotypes although some of the analytical methods and parameters have evolved since licensure. Manufacture of the seven new Polysaccharide (PS) serotypes differs in several ways from the 13vPnC serotypes. The new serotypes do not utilize (b) (4)



(b) (4)



All serotypes are (b) (4)



(b) (4)

The 20vPnC drug product (DP) is made and filled on the same equipment used for the 13vPnC DP and is presented in the same syringes and stoppers. A shelf-life of 24 months at 2-8°C has been proposed and is supported by data extending beyond 24 months on (b) (4) primary stability lots. Target DP batch sizes are (b) (4). One study to 24 months has been performed on a (b) (4) production lot and two other (b) (4) lots have stability data to 18 months. The longest stability study on a (b) (4) production lot at this time is 12 months.

Information requests (IRs) for CMC were predominantly relating to minor issues, such as requesting copies of batch records for a few 13vPnC serotypes and verifying resolution of leakage observed for some flexible containers. Major CMC issues involved lack of qualified master cell banks (MCBs) for 6A and 19A and the proposed (b) (4) for CRM<sub>197</sub>. The MCB issue began under the 13vPnC license for which the applicant has (b) (4)

In the comparability study of (b) (4) the applicant used an inappropriate statistical method. After consultation and review by a statistician, the company submitted an updated method as requested.

Pfizer submitted serologic data from three phase 3, one phase 2 and two phase 1 studies conducted with 20vPnC. Immunogenicity results in the three phase 3 trials were used to assess vaccine efficacy. The immunogenicity was evaluated by measuring serum opsonophagocytic activity (OPA) in a microcolony OPA (mcOPA) assay. Immunogenicity was also evaluated in the three phase 1 and 2 studies by using mcOPA and by the measurement of serum IgG antibody responses against the polysaccharides included in the 20vPnC in a (b) (4). However, the (b) (4) data will not be included in the package insert in support of vaccine efficacy.

Vaccine induced OPA activity was used in the licensure of 13vPnC by comparing the OPA titers induced by 13vPnC with the licensed 7-valent pneumococcal conjugate vaccine, Prevnar®. A similar approach is used in the evaluation of 20vPnC efficacy. The mcOPA titers elicited by 20vPnC are compared to the activity induced by 13vPnC for the thirteen shared serotypes. For the seven new serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) unique to 20vPnC, efficacy was assessed by comparing the mcOPA titers in 20vPnC and in 23-valent polysaccharide vaccine (PPSV23), Pneumovax23® immunized subjects. In both comparisons a non-inferiority to geometric mean titers (GMT) in 20vPnC was the primary immunological endpoint.

Comparison of mcOPA GMTs between 20vPnC and 13vPnC forms the basis of invasive pneumococcal disease (IPD) and pneumonia indications for 20vPnC because 13vPnC

is approved for the prevention of IPD and pneumonia in adults. For the seven new serotypes, comparison of mcOPA GMTs between 20vPnC and PPSV23 forms the basis of IPD indication because PPSV23 is approved for IPD. However, as part of the accelerated approval agreement, a pneumonia indication for the seven additional serotypes will also be granted if the non-inferiority comparisons between 20vPnC and PPSV23 are met. The accelerated approval agreement also requires Pfizer to present data from a confirmatory real-world observational effectiveness study with pre-specified endpoints measuring protection against pneumonia caused by the seven additional serotypes in adults  $\geq 65$  years of age.

Pfizer also presented mcOPA data against serotype 15C which is not a component of 20vPnC. Immune response to 15C was evaluated because of the structural similarity between the vaccine serotypes 15B and 15C. These two serotypes differ based on the presence of an O-acetyl group on serotype 15B, which is expressed in a small amount on serotype 15C. According to Pfizer, the presence of likely cross-reactive functional antibodies against serotype 15C in 20vPnC immunized subjects does not provide sufficient evidence of protection against pneumococcal disease due to serotype 15C. Therefore, Pfizer recognized that additional data will be necessary to determine if the cross-reactive OPA response is clinically meaningful.

When evaluating the immune response against serotype 11A for the three phase 3 studies in mcOPA, Pfizer conducted two separate analyses using lower limit of quantitation (LLOQ)s of (b) (4). During the review of validation results for serotype 11A as part of IND 17667 for 20vPnC submission, the LLOQ of (b) (4) proposed by Pfizer was not accepted because the precision data did not support this LLOQ. Pfizer was advised to use LLOQ of (b) (4) for serotype 11A. In line with CBER recommendation, initially Pfizer analyzed phase 3 clinical study results using a LLOQ of (b) (4) for serotype 11A. Subsequently, Pfizer submitted additional range extension study results for serotype 11A to IND 17667. CBER review concluded that the additional data supported the LLOQ of (b) (4) for serotype 11A. Thus, a second analysis of clinical data was conducted using (b) (4) as LLOQ for serotype 11A.

Several assay-related IRs were sent to Pfizer during the review of serology results. These IRs were primarily related to missing documents (i.e. SOPs) referenced in the validation studies. The IRs also included the request of data supporting the assay stability from the time of validation until the completion of the analysis of clinical samples. Sponsor adequately addressed these IR comments.

Overall, the submission was complete. The overall control strategy and the long history of Prevnar-7 and Prevnar-13 products assure consistent manufacture and product quality. Approval is recommended.



## B. RECOMMENDATION

### I. APPROVAL

Approval of this BLA will include Comparability Protocols for the (b) (4)

Updates will be reported in the Annual Report.

### II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Lisa Parsons, Ph.D./Biologist/DBPAP	Concur	
James Keller, Ph.D./Biologist/DBPAP	Concur	
Mustafa Akkoyunlu, M.D., Ph.D./Biologist/DBPAP	Concur	
Willie F. Vann, Ph.D./Supervisory Senior Research/DBPAP	Concur	
Jay E. Slater, M.D./ Supervisory Medical Officer/DBPAP	Concur	

## Review of CTD

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## **Module 1**

### **1.1 ADMINISTRATIVE INFORMATION AND PRESCRIBING INFORMATION**

#### **1.3.5.3 Exclusivity**

Reviewed by LP

The applicant filed a request for reference product exclusivity on 08 October 2020. Pfizer claimed there are no licensed biological products that are structurally related to the 20vPnC vaccine for which they or one of its affiliates, licensors, predecessors in interest, or related entities is the current or previous license holder. Pfizer does not believe that Prevnar 13® was relevant as it only contains thirteen of the twenty serotypes in the 20vPnC vaccine. We disagreed. The following IR was sent 26 January 2021.

#### **Exclusivity Information Request (IR-3)**

*We refer to your request submitted and received on October 8, 2020, regarding exclusivity. In order to assist Food and Drug Administration (FDA) in evaluating the date of first licensure as described in section 351(k)(7)(C) of the PHS Act for Pneumococcal 20-valent Conjugate Vaccine [Diphtheria CRM197 Protein], we have the following comments:*

- 1. Regarding your claim for product exclusivity in Section 1.3.5.3, we acknowledge your statement “that there are no licensed biological products that are structurally related to Pneumococcal 20-valent Conjugate Vaccine [Diphtheria CRM197 Protein]”, however as described in the 2014 Guidance for Industry (Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act) you should include all products that share any of the same principal molecular structural features of the product being considered, but generally can be limited to products that affect the same molecular target. As 13vPnC shares some of the same principle molecular structure features and targets as Prevnar20, we do not agree with your assertion that 13vPnC is not relevant.*

*Based on our advice, please revise your exclusivity claim and submit a list of all licensed biological products that are structurally related and/or that share some of the same principal molecular structural features to the biological product that is the subject of the 351(a) application being considered. If your assessment results in the conclusion that no products that have the same molecular target or share some of the same principal molecular structural features have been licensed, please provide an adequate justification to support the assertion that there are no previously licensed products that are relevant for purposes of determining the date of first licensure.*

2. *Of those licensed biological products identified in item 1 above, please identify the products for which you or one of your affiliates, including any licensors, predecessors in interest, successors in interest, or related entities are the current or previous license holder.*
3. *Please describe the structural differences between the biological product being considered and any products identified in item 2 above. For protein products, this should include, but is not limited to, changes in amino acid sequence, differences due to post-translational events, infidelity of translation or transcription, differences in glycosylation patterns or tertiary structure, and differences in biological activities.*
4. *Please provide evidence of the change in safety, purity, and/or potency between the proposed product and any products identified in item 2 above.*

A response was received 9 February 2021 and is under STN 125731/.14.

The company revised their submission as follows.

1. Prevnar 13 is structurally related to 20vPnC, but there are no licensed biological products that include polysaccharide-protein conjugates that are structurally related to the seven new serotypes in 20vPnC.
2. Wyeth Pharmaceuticals LLC (a subsidiary of Pfizer Inc.) or one of its affiliates, licensors, predecessors in interest, or related entities is the current or previous license holder for Prevnar 13.
3. The inclusion of the seven additional serotypes makes the 20vPnC vaccine unique both due to the antigenic distinctness of each new serotype and because all the antigens in a multivalent vaccine may immunologically interact. Reference was made to module 3 in the submission for structural information.
4. The addition of the seven new serotypes results in a change in potency as compared to Prevnar 13 since Prevnar 13 is not effective against the seven new serotypes. This is supported by both the clinical data in the submission and FDA's grant of both fast track designation and break through therapy designation.

### **Review of Response to the Exclusivity IR**

We agree that there are no currently licensed products other than Prevnar 13 that are structurally related to the 20vPnC vaccine. Pneumovax®23 contains twenty-three polysaccharides, most of which are in the 20vPnC vaccine, however they are not conjugated to protein and therefore have a very different immune response likely because they affect different molecular targets.

### **Determination of Exclusivity**

The 20vPnC vaccine is structurally and antigenically distinct from 13vPnC which has resulted in a change in potency. Even though it has the same sponsor as Prevnar 13, it qualifies to have its own date of first licensure due to the change in potency. Thus, pursuant to Section 351(k)(7)(A), no approval of an application submitted under Section 351(k) for which Pneumococcal 20-valent Conjugate Vaccine [Diphtheria CRM<sub>197</sub>

Protein] is the reference product can be made effective until 12 years after the date of licensure of Pneumococcal 20-valent Conjugate Vaccine [Diphtheria CRM<sub>197</sub> Protein]. In addition, pursuant to Section 351(k)(7)(B), no application under Section 351(k) for which Pneumococcal 20-valent Conjugate Vaccine [Diphtheria CRM<sub>197</sub> Protein] is the reference product can be submitted until 4 years after the date of licensure of Pneumococcal 20-valent Conjugate Vaccine [Diphtheria CRM<sub>197</sub> Protein].

CBER's reference product determination board met on 06 April 2021 and concurred with my recommendation to grant the designation. Upon approval, the product will be designated as a reference product and the associated exclusivity periods will be based upon the date of first approval

#### **1.12.14 Environmental Analysis**

By LP

Pfizer Inc. claims a categorical exclusion to the environmental assessment requirements in compliance with categorical exclusion criteria 21 CFR part 25.31 (c). This is appropriate for the polysaccharides and for CRM<sub>197</sub> since they are naturally occurring products.

### **Module 3**

#### **3.2.S DRUG SUBSTANCE**

(b) (4) [Redacted]




(b) (4) [Redacted]

[Redacted]





(b) (4)



### **3.2.P DRUG PRODUCT**

Reviewed by LP

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


The 20-valent Pneumococcal conjugate (20vPnC or Prevnar20) drug product consists of a mixture of the twenty conjugated DSs (monovalent bulk conjugates (MBC)) in a sterile liquid suspension in 1-mL glass, Leur 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 is formulated in (b) (4) succinate, (b) (4) sodium chloride, (b) (4) polysorbate 80 buffer, (b) (4) with (b) (4) aluminum as an adjuvant and no preservative. To ensure a nominal 0.5 mL volume can be administered, there is an overfill of (b) (4). There is no manufacturing overage.

#### **3.2.P.2 Pharmaceutical Development**

##### **3.2.P.2.1 Components of the Drug Product**

###### **3.2.P.2.1.1 Drug Substance**

(b) (4)



### 3.2.P.2.1.2 Excipients

Excipients are succinic acid, sodium chloride, (b) (4) aluminum phosphate, and polysorbate 80 (PS80). Succinate was chosen based on its ability to provide (b) (4). Sodium chloride (b) (4) effectively (b) (4). Aluminum phosphate is an adjuvant that helps achieve the desired immune response and PS80 (b) (4)

### 3.2.P.2.2 Drug Product

#### 3.2.P.2.2.1 Formulation Development

The 20vPnC DP was developed based on the formulation used for the 13vPnC vaccine. The amount of each serotype per dose and buffer systems are nearly the same except 20vPnC contains (b) (4) and the 20vPnC contains seven additional MBCs. The (b) (4) was (b) (4) to align with the Pfizer formulation platform. The container closure system is the same in both DPs and both DPs are filled on the same filling lines.

The target fill volume for 20vOnC vaccine is (b) (4) while the target deliverable volume is (b) (4). The syringe fill range to produce the appropriate target deliverable volume has been experimentally determined to be (b) (4). The minimum (b) (4) was tested in (b) (4) syringes using a worst-case needle size of (b) (4). At a minimum, (b) (4) was expelled onto a test scale with an average of (b) (4)

#### 3.2.P.2.2.2 Overages

Not Applicable

#### 3.2.P.2.2.3 Physicochemical and Biological Properties

Reviewed by LP

Excipients were chosen based on their use in 13vPnC vaccine, then further evaluated.

(b) (4)  
but remained within the process validation (PV) acceptance criteria until the (b) (4) was (b) (4) of what is proposed for the vaccine. The robustness

of the (b) (4) was demonstrated by measuring (b) (4)  
(b) (4). All values were within PV stability acceptance criteria.

The number of (b) (4) needed to (b) (4) after storage of the syringes in (b) (4) or horizontal orientations were compared. Median values were (b) (4) for horizontal and (b) (4) for (b) (4) leading to horizontal as the preferred method for storage.

### 3.2.P.2.3 Manufacturing Process Development

Reviewed by LP

The company submitted documents describing the Process Risk Assessment Strategy, the Control Strategy, and the Quality Attributes of the vaccine. Risk assessment included (b) (4)

(b) (4) Operating parameters and normal operating ranges (NORs) were established based on (b) (4)

Manufacturing changes during DP development included (b) (4)

(b) (4) After production of the nonclinical toxicology batches, manufacturing was transferred to and remains at the intended commercial manufacturing site. Batch size was (b) (4)

(b) (4) All batches used the same manufacturing process and equipment. (b) (4) different fill lines have been used for manufacture, are considered compatible, and are (b) (4) intended to be used for manufacture. Automated visual inspection was introduced in the (b) (4). Multiple supplier sites demonstrated comparable product for a wide variety of container closure sites.

The following process development studies were summarized in 3.2.P.2.3

(b) (4)

1. (b) (4)



(b) (4)

### 3.2.P.2.4 Container Closure System

Reviewed by LP

The 20vPnC vaccine is supplied in a prefilled syringe with an elastomeric plunger stopper. The syringe is made of (b) (4) borosilicate glass with a tip cap assembly that includes a Luer lock adapter, a rigid cap, and a product-contact elastomeric insert made of a (b) (4) rubber. Syringes are delivered sterile by (b) (4). The plunger stopper, made of (b) (4) rubber, is manufactured by (b) (4) and supplied sterile by (b) (4). Non-product contact components are the finger grip made by (b) (4) and the plunger rod manufactured by (b) (4). The syringe barrel and plunger stopper are (b) (4). The syringe design and packaging of the 20vPnC vaccine are identical to those of the 13vPnC vaccine.

Commercial syringes are manufactured in (b) (4)

Commercial stoppers are from (b) (4). The syringe and

stopper components are considered interchangeable based on comparability of incoming components, manufacturability of component combinations, and product stability. (b) (4) components are manufactured to the same specifications at all sites with the same raw materials. (b) (4) syringes are dimensionally comparable and use the same materials of construction. All components met safety requirements for biological activity and biocompatibility.

(b) (4)

Several tests were used to verify the design of the syringe. These included, (b) (4) leachable studies. Some of these are described elsewhere in this memo, those unique to 3.2.P.2.4: *Container Closure System* are below.

Manufacturability was evaluated by the ability of the (b) (4)

This was demonstrated by (b) (4) testing (see 3.2.P.2.5) and media fills on (b) (4) different fill lines. All lots except (b) (4) had comparable reject rates during automated visual inspection. Lot (b) (4) had a higher apparent rate due to an equipment issue.

The vendor performed extraction studies on the elastomeric plunger stopper and tip cap material for (b) (4)

To demonstrate protection from light, the company (b) (4). None of the quality attributes were affected. They also validated the container closure system as integral (see 3.2.P.2.5: Microbiological Attributes).

Syringeability refers to the force required for the injection of a given solution at a given rate via a needle of predetermined gauge and length and is attributed to the (b) (4). (b) (4) is considered to be the maximum acceptable injection force and (b) (4) is the target. The company demonstrated (b) (4) were below (b) (4). All results were comparable.

Product design in terms of user need was validated by comparing the primary operating function or user guide instruction to the criticality of performing the function and the outcome in the event of error. For example, what is the outcome if the user fails to shake the syringe vigorously prior to injection? The company concluded that since health care providers are familiar with the required tasks and since the 20vPnC vaccine is packaged and administered like the 13vPnC vaccine which has been on the market since 2010, a human factors validation study was not required.

Product risk analysis to the patient or user was performed. Risks assessed included design-related risks (i.e. (b) (4)), use-related risks (i.e. (b) (4)), and process-related risks (i.e. (b) (4)). Potential failures, hazardous situations, possible harm, and benefit-risk analysis discussion are in table 3.2.P.2.4-19: *Risk Benefit Analysis Summary of Residual Risks* in 3.2.P.2.4: *Container Closure System*. It was concluded that the use of the product outweighs the risk.

### 3.2.P.2.5 Microbiological Attributes

Reviewed by LP

The 20vPnC DP is a single dose sterile liquid suspension with no preservatives. A (b) (4) examination found the DP formulation to be (b) (4). DP is tested for sterility and endotoxin on release (b) (4). The container closure system (CCS) and its components were selected based on their ability to protect the quality of the product over its shelf life. (b) (4) testing was used to qualify the integrity of the CCS.

(b) (4) testing was performed on all combinations of syringes (b) (4) and plunger stoppers (b) (4).



(b) (4) for a total of (b) (4) combinations. (b) (4) syringes  
(b) (4)  
All test syringes had no  
visible evidence of (b) (4).

### **3.2.P.2.6 Compatibility**

Reviewed by LP

The compatibility of the 20vPnC vaccine with the syringe container closure system (CCS) was determined based on primary stability studies (see 3.2.P.8.1) where the syringe was stored in a horizontal position to enable product contact on all surfaces of the syringe. Stability data demonstrated the 20vPnC vaccine remained within the established acceptance criteria under the recommended storage conditions.

Syringe compatibility with DP components was demonstrated by (b) (4)

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

Reviewed by LP: I found no deficiencies in Section 3.2.P.2

### **3.2.P.3 Manufacture**

Reviewed by LP

#### **3.2.P.3.1 Manufacturer(s)**

Manufacturing responsibilities for  $\text{AlPO}_4$  suspension and the 20vPnC vaccine are in Table 1-1 of this document.

#### **3.2.P.3.2 Batch Formula**

The target DP batch sizes are (b) (4). Each (b) (4) batch has (b) (4) of each serotype except 6B (b) (4) and each (b) (4) batch has (b) (4) of each serotype except 6B (b) (4). Other ingredients for the (b) (4) batch sizes are aluminum phosphate (b) (4) aluminum), succinic acid (b) (4), sodium chloride (b) (4) sufficient to reach (b) (4) polysorbate 80 (b) (4) and (b) (4) sufficient to reach (b) (4), respectively.

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

Reviewed by LP: I found no deficiencies for Sections 3.2.P.3.1 and 3.2.P.3.2. The information is acceptable as submitted.

### **3.2.P.3.3 Description of Manufacturing Process**


(b) (4)

(b) (4)

(b) (4)

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

(b) (4)

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

Reviewed by LP: I found no deficiencies for Sections 3.2.P.3.3. The information is acceptable as submitted.

**3.2.P.3.4 Controls of Critical Steps and Intermediates**

The following refers to information in 3.2.P.3.3. In-process test (IP-T) acceptability criteria for critical steps and hold times are listed with the descriptions above in 3.2.P.3.3.

(b) (4)

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A rectangular area of the document is redacted with a solid gray fill.  
A large rectangular area of the document is redacted with a solid gray fill.

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

(b) (4)

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

Reviewed by LP: I found no deficiencies for Section 3.2.P.3.4. The information is acceptable as submitted.

**3.2.P.3.5 Process Validation and/or Evaluation**


Control of the 20vPnC DP manufacturing process was demonstrated by maintaining process parameters within the defined normal operating ranges specified in the manufacturing batch records. Process validation (PV) acceptance criteria included all critical process parameters and non-critical parameters and outputs based on early process and parameter evaluations and pre-PV experience. Process performance assessments included the (b) (4)

These are each described in more detail below.

(b) (4)



(b) (4)



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

Reviewed by LP: I found no deficiencies for Section 3.2.P.3.5. The information is acceptable as submitted.


#### **3.2.P.4 Control of Excipients**

Reviewed by LP

##### **3.2.P.4.1 Specifications**

Excipients succinic acid, sodium chloride, polysorbate 80, and (b) (4) are compendial. Specifications will be maintained to comply with the current version of the (b) (4).

AlPO<sub>4</sub> suspension is the only non-compendial excipient. Specifications are aluminum concentration (b) (4) description (b) (4)




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

The procedures below all apply to the AlPO<sub>4</sub> suspension.



(b) (4)

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#### **3.2.P.4.4 Justification of Specifications**

The acceptance criteria for  $\text{AlPO}_4$  is based upon (b) (4) requirements and statistically analyzed historical manufacturing process performance of at least (b) (4) lots manufactured in (b) (4).

#### **3.2.P.4.5 Excipients of Human or Animal Origin**

There are no excipients of human or animal origin

#### **3.2.P.4.6 Novel Excipient**

There are no novel excipients

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

Reviewed by LP: I found no deficiencies for Section 3.2.P.4. The information is acceptable as submitted.

### 3.2.P.5 Control of Drug Product

Reviewed by LP

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

**Table 15: 20vPnC Drug product specifications**

Quality Attribute	Analytical procedure	Acceptance criteria
Aluminum concentration	(b) (4)	(b) (4)
(b) (4)		(b) (4)
Total protein concentration		(b) (4)
Appearance	visual inspection	homogeneous, white suspension (R,S)
Container Closure integrity <sup>2</sup>	(b) (4)	(b) (4)
Identity (Saccharide/CRM <sub>197</sub> )	(b) (4)	(b) (4)
(b) (4) PS80	(b) (4)	(b) (4)
(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)

<sup>1</sup> R=used for release, S=used for stability

<sup>2</sup> Container closure integrity will be used *in lieu* of the sterility test during stability studies

<sup>3</sup> See Table 16-1,-2,-3.

<sup>4</sup> For the 13vPnC vaccine, (b) (4) protein is (b) (4) and (b) (4) is (b) (4)

20vPnC DP specifications for release and stability are in Table 15. Up to (b) (4) different lots from different stages of development (i.e. clinical, phase 3) were evaluated to establish acceptance criteria (AC) specifications. Where relevant, the mean and standard deviation were calculated and tolerance interval (TI) levels set to (b) (4) standard deviations of the population at a 95% confidence level, then adjusted based on experience, robustness studies, stability studies, and historical knowledge of 13vPnC DP.

Some AC values applied for the 13vPnC serotypes used in 20vPnC differ from those in the 13vPnC vaccine. The (b) (4) in 20vPnC based on

robustness studies. The AC for (b) (4) . This is acceptable as the company found (b) (4) (See 3.2.P.2.2.3).

There are multiple differences in the (b) (4) AC between the two vaccines. AC in 20vPnC that differ from those in 13vPnC are highlighted gray under the 20vPnC columns in Tables 16-1, 2, 3. For the (b) (4) , most AC are more stringent or change very little. A total of (b) (4) serotypes have (b) (4) release AC for (b) (4) as compared to 13vPnC but only (b) (4) have (b) (4) stability AC. The largest (b) (4) in release AC was (b) (4) for serotypes (b) (4) . The new values are based on TI calculated from real data. Although many values are (b) (4) , the AC for (b) (4) stability are reasonable based on the data. Serotypes not in 13vPnC are also highlighted in gray.

**Table 16-1: Comparison of release and stability acceptance criteria for 13vPnC and 20vPnC** (b) (4)

(b) (4)				
Serotypes	13vPnC		20vPnC	
	release	stability	release	stability
1	(b)	(4)	(b)	(4)
3				
4				
5				
6A				
6B				
7F				
8				
9V				
10A				
11A				
12F				
14				
15B				
18C				
19A				
19F				
22F				
23F				
33F				

<sup>1</sup> Serotypes in gray are only in 20vPnC vaccine. 20vPnC criteria in gray differ from the 13vPnC criteria.

**Table 16-2: Comparison of release and stability acceptance criteria for 13vPnC and 20vPnC** (b) (4)

(b) (4)				
Serotypes	13vPnC		20vPnC	
	release	stability	release	stability
1	(b) (4)			
3				
4				
5				
6A				
6B				
7F				
8				
9V				
10A				
11A				
12F				
14				
15B				
18C				
19A				
19F				
22F				
23F				
33F				

<sup>1</sup> Serotypes in gray are only in 20vPnC vaccine. 20vPnC criteria in gray differ from the 13vPnC criteria.

**Table 16-3: Comparison of release and stability acceptance criteria for 13vPnC and 20vPnC**

	(b) (4)			
	(b) (4)			
	13vPnC		20vPnC	
<b>Serotypes</b>	<b>release</b>	<b>stability</b>	<b>release</b>	<b>stability</b>
1	(b) (4)			
3				
4				
5				
6A				
6B				
7F				
8				
9V				
10A				
11A				
12F				
14				
15B				
18C				
19A				
19F				
22F				
23F				
33F				


<sup>1</sup> Serotypes in gray are only in 20vPnC vaccine. 20vPnC criteria in gray differ from the 13vPnC criteria.

Below is a summary of the quantitative parameters and how the AC were derived.

**Aluminum concentration** is quantitated by (b) (4) in comparison to an aluminum (b) (4). It had a calculated TI of (b) (4). Based on robustness studies and experience with 13vPnC DP, the value was adjusted to (b) (4).

**Total protein concentration** is measured using the (b) (4) as described for the (b) (4) is eliminated by (b) (4). Calculated TI was (b) (4), but the theoretical range based on the AC for each (b) (4) is (b) (4). The company chose an AC value between them of (b) (4).


(b) (4)



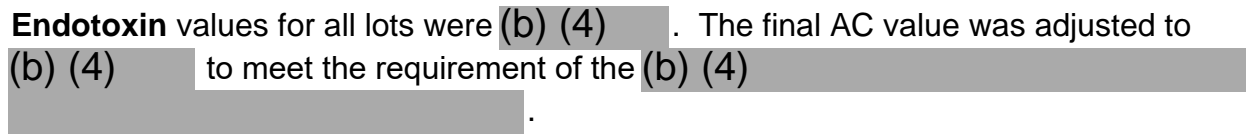
**PS80** concentration is measured by using (b) (4)






(b) (4)




**Endotoxin** values for all lots were (b) (4). The final AC value was adjusted to (b) (4) to meet the requirement of the (b) (4).



(b) (4)



(b) (4)





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

Reviewed by LP: I found no deficiencies for Sections 3.2.P.5.1 and 3.2.P.5.6. The information is acceptable as submitted.

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

Analytical methods for release tests are listed in Table 15. Methods not reviewed here are referred to DBSQC.






(b) (4)

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(b) (4)



#### **Overall Reviewer's Assessment of Sections 3.2.P.5.2 and 3.2.P.5.3:**

Reviewed by LP: I found no deficiencies for Sections 3.2.P.5.2 and 3.2.P.5.3. The information is acceptable as submitted.

#### **3.2.P.5.4 Batch Analyses**

Values for (b) (4) batches with batch sizes of (b) (4)

used for nonclinical toxicology, engineering, clinical, stability, and process validation were submitted. All but the (b) (4) batches were made a (b) (4)

The (b) (4) batches were made in (b) (4)

(b) (4) were used for nonclinical toxicology. Data did not show any trends.

### 3.2.P.5.5 Characterization of Impurities

The company states, "There are no known process-related impurities associated with DP formulation and filling". Degradation of the DP could lead to product-related impurities due to degradation of the (b) (4) breakdown products. (b) (4) levels are monitored during stability and assessed against acceptance criteria.

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

Reviewed by LP: I found no deficiencies for Sections 3.2.P.5.4 and 3.2.P.5.5. The information is acceptable as submitted.

### 3.2.P.6 Reference Standards or Materials

Reviewed by LP

The 20vPnC vaccine uses a (b) (4) reference material (RM) for all the DP (b) (4) assays to quantitate the (b) (4) of each individual serotype in the vaccine. The RM is (b) (4) with (b) (4) of each conjugate except for serotype 6B of which (b) (4) is used, in a (b) (4) sucrose, (b) (4) succinate, (b) (4) pPS80, in (b) (4) at (b) (4). The RM is (b) (4).

(b) (4)

(b) (4)

### 3.2.P.7 Container Closure System

Reviewed by LP

The primary container closure system for 20vPnC consists of a 1 mL glass syringe barrel closed with a tip cap and a plunger stopper. A description of the components, extractables and leachables, and syringeability can be found under 3.2.P.2.4:

*Pharmaceutical Development-Container Closure System.* Syringes are sterilized by

(b) (4) and received at the DP manufacturing site (b) (4). The addresses of the manufacturing and sterilization sites of the plungers and syringes are listed in Tables 3.2.P.7-2, 3, and 8 in the submission. Syringes are made by (b) (4). While not identical, the dimensions are comparable, and all parts are considered interchangeable as described in 3.2.P.2.4. Drawings and a comparison of the dimensions were included. Quality control of the syringe barrel on each lot includes visual inspection of the syringe package and barrel, physical inspection of the barrel, and functionality testing of the syringe. (b) (4) glass tests, (b) (4) are certified by the manufacturer on each lot. The company performs (b) (4) verification on (b) (4) to ensure testing requirements are met. Studies and data to demonstrate integrity of the product during shipping are under 3.2.P.2.3 *Manufacturing process development*.

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

Reviewed by LP: I found no deficiencies for Sections 3.2.P.7. The information is acceptable as submitted.

### 3.2.P.8 Stability

Reviewed by LP

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

The shelf life of 20vPnC DP is 24 months when stored at 2-8°C based on stability data from (b) (4) primary stability lots stored in the horizontal position. Stability data from (b) (4) other DP lots was also included in the submission. Data is from long term, (b) (4) (b) (4) studies (defined in Table 17). Lot, size, date of manufacture, and tests done are in Table 18. Completed studies are in green.

(b) (4)

**Table 18: *Stability lots***

(b) (4)

Quality attributes followed for long-term studies at 2-8°C: (b) (4), total protein concentration, appearance, container closure integrity, (b) (4), endotoxin, sterility, (b) (4)

(b) (4) tests after the primary stability lots were put on stability, so results (b) (4) are included. The company included plots of all the data for the different quality attribute values for the long-term studies. (b) (4)

(b) (4) while total protein and (b) (4) remain steady. After 24 months at 2-8°C, the company noted changes in the (b) (4) results for most serotypes, (b) (4) were obvious (figures 3.2.P.8.3-5, 10, and 20 under 3.2.P.8.3: *Stability Data – Long term stability data.*). All measurements met the acceptability criteria. (b) (4) for

serotype (b) (4) but (b) (4)

Accelerated studies at (b) (4) have been completed for (b) (4) DP lots. (b) (4)

Under (b) (4) stress conditions of (b) (4)

DP that underwent (b) (4)

The company has submitted data for (b) (4) lots and (b) (4) covering at least twenty-four months post-manufacture that shows the measured attributes stay within the AC. They've also demonstrated the ability of their (b) (4) tests to detect aging of the vaccine with (b) (4) stress and accelerated storage experiments. The proposed shelf-life of twenty-four months is acceptable.

Under 3.2.P.3.5 *Process Validation and/or Evaluation*, the company indicated three process validation lots, (b) (4), were manufactured at cumulative maximum allowable process step holds during packaging and shipping. Those three lots currently have only (b) (4) of stability data. Under accelerated conditions (b) (4), all QA for these lots except (b) (4)

(b) (4)

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

The company commits to enrolling (b) (4) of 20vPnC vaccine in the commercial stability program at the long-term storage condition of  $5\pm 3^{\circ}\text{C}$  each year the DP is manufactured. The studies will be performed on syringes stored to reflect the final packaging configuration. (b) (4), total protein concentration, appearance, container closure integrity, (b) (4), endotoxin, sterility, (b) (4) will be monitored over (b) (4) months. Testing intervals are 0, 3, 6, 9, 12, 18, 24, (b) (4) months except for container closure integrity at 12, 24, (b) (4) months and endotoxin and sterility at (b) (4). Container closure integrity testing is used *in lieu* of sterility. Acceptance criteria can be found in 3.2.P.8.2: *Post-approval stability protocol and stability commitment*.

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

Reviewed by LP: I found no deficiencies for Section 3.2.P.8. The information is acceptable as submitted.

## **3.2.A APPENDICES**

### **3.2.A.2 Adventitious Agents Safety Evaluation**

Reviewed by LP.

20vPnC is not a viral product. Several ingredients are of animal origin as discussed previously so there is a theoretical risk of contamination by agents from Transmissible Spongiform Encephalopathy (TSE). The company has appropriately assessed the risks and controls needed. See section 3.2.S.2.3 for review.

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

Reviewed by LP: I found no deficiencies for Sections 3.2.A.2. The information is acceptable as submitted.

### **3.2.R Regional Information (USA)**

Reviewed by LP

### Executed Batch Records

Batch records were included for all of the new serotypes. The values for (b) (4) times, and other parameters matched what was submitted elsewhere, however many of the hold times did not match. For example, the (b) (4) for all the new serotypes, yet the batch records for both serotypes 8 and 33F set a time of (b) (4). An IR was sent 7 December 2020 requesting representative batch records of the 13vPnC records. A clarification request was received on 11 December 2020 and a final response on 16 December 2020. Records for serotype 4 and 6A were provided (See below). The values in the 13vPnC serotypes appear to match the submission.

### Comparability Protocols

Comparability protocols (CP) for preparation, qualification, storage, and shipping of future WCBs for all the 13vPnC serotypes that currently have MCBs: 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F, and for CRM<sub>197</sub> were submitted. Qualification involves testing for (b) (4). The company plans to report new WCB lots for all serotypes and CRM<sub>197</sub> in annual reports to the BLA. This is acceptable.

A CP for *Introduction of mammalian and animal derived (b) (4) and bacterial derived products and related raw materials into the common commercial areas, (b) (4) facility* was submitted. The Pfizer (b) (4) facility was initially licensed for 13vPnC as a single host (bacteria) multi-product manufacturing facility for bacteria-derived vaccines. In 2018, (b) (4) introduced the capability to manufacture (b) (4) (referenced to STN 125324/1770)). The manufacturing areas for the (b) (4) products are separate from the bacterial ones, with separate heating, ventilation, air conditioning and support services. However, they do share common corridors and basic operating infrastructures such as the warehouse, raw material sampling suite and central dispensing area, QC laboratories, cell bank storage area, and the central utilities space. The impact of the new products on existing products in the shared facility and the (b) (4)-way cross-contamination risk was evaluated. This CP describes the risk assessment controls, standard procedures, and product evaluation requirements currently in use at Pfizer, (b) (4). The listed procedures include cleaning protocols and protocols for separate storage, weighing, and transportation of components for different products. Upon approval, Pfizer proposes to notify CBER of the initial introduction of future bacterial derived and (b) (4) DSs and DPs to the 20vPnC annual report. Since this is already approved under 13vPnC, this CP is acceptable.

### Lot Release

All values in the lot release match those in the submission for the PSs, MBCs, and DP. A major change between the 13vPnC and new serotypes is the lack of release information for the activated polysaccharides, specifically (b) (4). The values are reported as part of in-process tests for the new



serotypes instead of release values as for the 13vPnC serotypes. This is because the 13vPnC serotypes can be (b) (4)

The lot release protocol is referred to DBSQC for further review.

### **Information Request (IR-1)**

Reviewed by LP

#### **IR-1 Question Sent 7 Dec 2020**

We acknowledge the comments in the 16 Mar 2020 pre-BLA meeting question 5 in which we concurred with your proposal to only include batch records listed in Table 44 of your background material package. However, we have reconsidered and feel that a complete record of drug substance intermediates used in the manufacture of your drug product is needed for review. Please submit executed batch records for Pneumococcal Polysaccharide and Monovalent Bulk Conjugate serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F used during the manufacture of drug product process validation lot (b) (4). Please also include a representative batch record for CRM<sub>197</sub> manufactured by the process that utilizes casamino acid-yeast extract (CY process).

#### **Response to IR-1 Question**

Received 7 Dec 2020

The company hesitated to send 20,000 pages of additional documents especially since they are regularly inspected and asked why the batch records were needed.

#### **Clarification to IR-1 Question**

Sent 11 Dec 2020

Regarding your query about CMC question 2 in our information request dated 07 December 2020, the reason we requested batch records for the thirteen serotypes included in Prevnar 13 (STN 125324) is due to the age of the batch records in the file, which are over a decade old. Changes to the process may have occurred over time and the process and batch records on file under STN 125324 may not be identical to batch records currently used in production. We recognize your concern over the amount of documentation our request may require, therefore we will limit our request to two serotypes and CRM<sub>197</sub> (CY process) with the understanding we may request more in the future. Please submit executed batch records for Pneumococcal Polysaccharide and Monovalent Bulk Conjugate serotypes (b) (4) used during the manufacture of drug product process validation lot (b) (4). Please also include the batch record for CRM<sub>197</sub> batch lot (b) (4), manufactured by the process that utilizes casamino acid-yeast extract (CY process).

**Response to Clarification to IR-1 Question**

The company had already begun putting together the batch record for CRM<sub>197</sub> that utilized the CRM process (batch lot (b) (4)) and asked if they could submit that instead of the requested batch (b) (4). CBER agreed.

**Final response to IR-1 Question**

Received 16 Dec 2020

The company submitted the executed batch records for serotypes (b) (4) used during the manufacture of DP lot (b) (4) along with the batch records for CRM<sub>197</sub> CY process batch (b) (4).

**Review of response to IR-1 Question**

Reviewed by LP

The submitted batch records for (b) (4) appear complete and the processing parameters match those submitted. This is acceptable.

Reviewed by EK

Executed batch records were also included for DM and CY CRM<sub>197</sub> manufacture describing all stages of manufacture: (b) (4)

(b) (4) The batch records were reviewed and are acceptable.

## **Modules 4 and 5**

### **4.5. Nonclinical and Clinical Study Reports**

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

Reviewed by MA

#### **Summary**

Pfizer is seeking licensure of a vaccine composed of 20 valent (1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F) pneumococcal polysaccharide conjugated to CRM<sub>197</sub> (20vPnC). The 20vPnC serotypes 1, 3, 4, 5, 6A, 6B, 7F, 19A, 9V, 14, 18C, 19F, and 23F are also included in the licensed Pfizer pneumococcal polysaccharide conjugate vaccine, 13vPnC (13vPnC). The proposed indication for 20vPnC is active immunization for the prevention of invasive pneumococcal disease (IPD) and pneumonia 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. The efficacy of 20vPnC was assessed by measuring the serum immune responses against the vaccine serotypes of *S. pneumoniae*.

#### **Clinical studies**

Pfizer submitted data from three phase 3, one phase 2 and two phase 1 studies conducted with 20vPnC.

Phase 3 studies: B7471007, B7471008, and B7471006.

Phase 2 study: B7471002.

Phase 1 studies: B7471001 and B7471005.

Microcolony opsonophagocytic assay (mcOPA) titers in the three phase 3 trials were used to assess vaccine efficacy. In addition to mcOPA analysis, a (b) (4) was used in the evaluation of immune responses in the three phase 1 and 2 studies. This section covers the review of serology results from the clinical studies and the adequacy of mcOPA assay used in support of the vaccine efficacy claims. The (b) (4) is also evaluated as part of the review of phase 1 and 2 studies but not in depth since the data from phase 1 and 2 studies are not included in the package insert to claim vaccine efficacy.

#### **Phase 3 studies**

**B7471007 (Pivotal noninferiority study):** This study was conducted in three cohorts of subjects. Pivotal noninferiority was assessed in the subjects from the first cohort. In the first cohort, pneumococcal vaccine naïve adults ≥ 60 years of age received one dose of

20vPnC or 13vPnC. Twenty-eight to 42 days after the first dose, subjects who received 20vPnC were given saline and subjects who received 13vPnC were given PPSV23 (13vPSV/PPSV23 group). Noninferiority comparisons in mcOPA GMTs measured one month after the first dose were made between 20vPnC and 13vPnC for the thirteen shared vaccine serotypes and between 20vPnC and PPSV23 for the seven additional vaccine serotypes. Noninferiority was declared for a serotype if the lower bound of the 2-sided 95% CI for the ratio of OPA GMTs (geometric mean [titer] ratio [GMR]; 20vPnC to control) was  $> 0.5$  (2-fold criterion). Although the GMTs were lower for all serotypes except serotype 14 in 20vPnC immunized subjects than that of 13vPnC group, noninferiority was met for all thirteen common serotypes. Additional analyses of the two groups in cohort 1 by comparing the geometric mean fold rise (GMFR) from before to one month after vaccination, by assessing the proportion of subjects achieving  $\geq 4$  fold-rise in mcOPA titers from before to one month after vaccination, and by assessing the proportion of subjects achieving mcOPA titers  $\geq$  LLOQ at one month after vaccination compared with before vaccination indicated that 20vPnC and 13vPnC elicited comparable results for the thirteen common serotypes.

For the seven additional serotypes, comparison of mcOPA GMT between the two groups indicated that six serotypes in 20vPnC injected subjects were noninferior to those induced by PPSV23. Serotype 8 did not meet the noninferiority criterion because the GMR was 0.55 (95% CI: 0.49, 0.62), which is slightly above the two-fold margin. Additional analyses of serotype 8 immune responses indicated that the responses in 20vPnC group was consistently lower compared to those in the 13vPnC/PPSV23 group. For example, GMFR from before to one month after vaccination was 22.1 and 40.4 for 20vPnC group and 13vPnC/PPSV23 group, respectively. Also, 77.8% of subjects achieved a  $\geq 4$ -fold rise in mcOPA titers from before to one month after vaccination for serotype 8 in 20vPnC group compared to 86.8% in 13vPnC/PPSV23 group. Finally, 93% of subjects had mcOPA titers  $\geq$  LLOQ for serotype 8 in 20vPnC compared to 96.6% in 13vPnC/PPSV23 group. The clinical meaning of not meeting the noninferiority criterion and the consistently lower responses in other analyses for serotype 8 is not known. Pfizer argued that the serotype 8 specific mcOPA titers elicited by 20vPnC are likely sufficient to provide substantial protection against pneumococcal infection due to serotype 8 because the results of the analyses for serotype 8 are comparable to those for the thirteen serotypes in subjects immunized with the 13vPnC vaccine. Since there is no established serotype specific mcOPA titer predictive of protection, it is not possible to draw a definitive conclusion about the protective value of mcOPA titers by comparing serotype 8 titers with the titers against other serotypes. Nevertheless, considering that the noninferiority criterion was narrowly missed, the mcOPA titers elicited by 20vPnC indicate the vaccine is likely sufficient to provide substantial protection against serotype 8 pneumococcal infection over vaccine naïve individuals. For the remaining 19 serotypes, serological responses elicited by 20vPnC was noninferior to those induced by PPSV23.

Study B7471007 (cohort 1) also included bridging analysis to compare the responses to 20vPnC in adults 50 through 59 years of age (cohort 2) as well as in adults 18 through 49 years of age (cohort 3) to those in adults 60 through 64 years old for the 20

serotypes in 20vPnC. Responses measured one month after the administration of vaccines indicated that the mcOPA titers in cohort 1 were noninferior to the responses in cohorts 2 and 3 as demonstrated by the lower bound of the 2-sided 95% CIs for the primary analysis of model-based OPA GMRs  $> 0.5$ . Additional sensitivity analysis also indicated that responses to all 20 serotypes were comparable in all three cohorts.

Study B7471007 had two exploratory objectives. In the first exploratory objective, cohort comparisons were made between subjects with and without risk factors. Subjects in cohorts 1, 2, and 3 with diabetes mellitus, asthma, chronic heart disease, and cigarette smokers were included in this analysis. At risk and healthy subjects' mcOPA titers were compared for GMFR, percent of subjects with  $\geq 4$ -fold rise, and percent of subjects with titers  $\geq$  LLOQ. For all three comparisons, responses of subjects with risk-factors were consistently lower than those without risk-factors. However, the differences between the two groups of subjects were not high enough to suggest insufficient response.

In the second exploratory objective, cross-functional antibody response against serotype 15C, which shares structural similarity with the 20vPnC serotype 15B, was measured in mcOPA analysis. In all three cohorts, subjects receiving 13vPnC did not develop cross-functional response to serotype 15C whereas subjects who received 20vPnC did. However, comparisons for GMFR, percent of subjects with  $\geq 4$ -fold rise, and percent of subjects with titers  $\geq$  LLOQ indicated that responses against serotype 15C was substantially lower than the responses against the vaccine serotype 15B.

**B7471008 (Clinical lot consistency study):** To assess lot consistency, immune responses elicited by three manufacturing lots of 20vPnC were compared to each other. The study population included 18 to 49-year-old adults. Serum mcOPA titers were measured one month after vaccination. The 20vPnC vaccines lots administered were 18-001439, 18-002741, and 18-002653. Equivalence was declared for a given serotype if the 2-sided 95% CI for the serotype-specific OPA GMR for each pair of lot comparisons (Lot 1/Lot 2, Lot 1/Lot 3, and Lot 2/Lot 3) was contained in the prespecified interval (0.5, 2.0). All 20 serotypes met the prespecified criterion. In additional sensitivity analyses, GMFR, proportion of subjects achieving a  $\geq 4$ -fold rise in mcOPA titers from before to one month after vaccination and proportion of subjects with mcOPA titers  $\geq$  LLOQ were similar for all 20 serotypes and for serotype 15C between the three lots.

**B7471006 ( $\geq 65$  years of age with previous pneumococcal vaccination history):** Immunogenicity of 20vPnC in subjects with previous history of pneumococcal vaccination was evaluated in study B7471006. Responses in this study were subjected to descriptive analyses. Three groups of subjects who had previously received pneumococcal vaccines were included in this study. Adults  $\geq 65$  years of age previously vaccinated with PPSV23 (cohort A) 13vPnC (cohort B), or 13vPnC followed by PPSV23 (cohort C) were vaccinated with 20vPnC. Subjects in cohort A were vaccinated with PPSV23  $\geq 1$  year and  $5 \leq$  years prior to vaccination with 20vPnC and had no prior 13vPnC vaccination history. Subjects in cohort C had received the 13vPnC  $\geq 6$  months prior to vaccination with 20vPnC and had no prior PPSV23 vaccination history. Subjects in cohort C had received their PPSV23  $\geq 1$  year prior to vaccination with 20vPnC.

Serum mcOPA titers were measured prior to and one month after vaccination with 20vPnC. The primary immunogenicity objective of the study was to describe the serotype specific mcOPA titers one month after the vaccination. The levels of baseline mcOPA titers varied depending on previous vaccination history. Although all groups elicited substantial increases in mcOPA titers after vaccination with 20vPnC, there were differences between cohorts. Cohort A had the lowest post-vaccination GMTs for all 20 serotypes compared to the other two cohorts. Subjects in cohort B had the highest GMTs for all 20 serotypes. It is noteworthy that subjects in cohort A, who had previously received the seven additional serotypes in PPSV23 mounted lower GMTs after vaccination with 20vPnC than those in cohort B even though the subjects in cohort B had been vaccinated with 13vPnC were naïve to the seven additional serotypes. These results underscore the blunting of host response to a booster immunization in subjects who have previously experienced a vaccine containing T cell independent antigens such as PPSV23.

The study had three secondary objectives. The first was to describe the GMFR in serotype-specific mcOPA titers from before to one month after vaccination. The GMFRs for the 13vPnC serotypes were generally highest in cohort B who had received the 13vPnC previously. Subjects in cohort B had the highest GMFRs for the seven additional serotypes also, mostly because they had lower pre-immune titers than the subjects in the two other cohorts and they elicited higher GMTs after 20vPnC vaccination. There was no notable difference in the GMFRs between cohorts A and C. The second of the secondary objectives was to describe the proportion of subjects with  $\geq 4$ -fold rise in serotype-specific mcOPA titers from before to one month after vaccination. For most of the 13vPnC serotypes, the proportions of participants who achieved a  $\geq 4$ -fold rise in mcOPA titers from before to one month after 20vPnC were generally higher in cohort B than the other two cohorts. The lowest proportion of participants who achieved a  $\geq 4$ -fold rise in mcOPA titers for the 13vPnC serotypes after receiving 20vPnC was in cohort C. For the seven additional serotypes, the proportions of participants with a  $\geq 4$ -fold rise in mcOPA titers from before to one month after 20vPnC were highest in cohort B. The third of the secondary objectives was to describe proportion of subjects with serotype specific OPA titers  $\geq$  LLOQ one month after vaccination. Cohort B had the highest proportion for this objective also.

Immunogenicity analysis for serotype 15C response was an exploratory objective for this study. The proportion of subjects with a  $\geq 4$ -fold rise in mcOPA titers for serotype 15C in cohorts A, B, and C were 9%, 19.5%, and 11.7%, respectively. These proportions were markedly lower than the proportions for the related serotype 15B in 20vPnC; they were 37.4%, 66.3%, and 38.4% for cohorts A, B, and C, respectively. Similarly, the proportion of subjects in cohorts A, B, and C with mcOPA titers  $\geq$  LLOQ one month after vaccination were lower for serotype 15C than those of serotype 15B.

## **Phase 2 Study**

**B7471002 (Immunogenicity in adults 60 through 64 years of age):** In study B7471002, in addition to safety, immunogenicity was evaluated in adult subjects 60

through 64 years of age who received 20vPnC or 13vPnC. One month later, those who received 20vPnC were injected with saline placebo while subjects in 13vPnC group received PPSV23. Immune responses were evaluated as secondary and exploratory objectives of the study. Blood samples were analyzed for immunogenicity, prior to each vaccination, one month after the first vaccination, one after the second vaccination and 12 months after the first vaccination. Functional antibodies were assessed by mcOPA and (b) (4) was used to measure IgG antibodies against the 20 pneumococcal serotypes.

#### *Secondary Endpoints*

- To describe pneumococcal serotype-specific mcOPA GMTs measured one month after vaccination.
- To describe pneumococcal serotype-specific mcOPA GMFRs measured from before vaccination to one month after vaccination.

#### *Exploratory Endpoints*

- To describe the proportion of subjects with pneumococcal serotype-specific mcOPA titers  $\geq$  LLOQ measured one month after vaccination.
- To describe pneumococcal serotype-specific IgG geometric mean concentrations (GMCs) measured, one month and 12 months after vaccination.
- To describe pneumococcal serotype-specific mcOPA GMTs 12 months after vaccination.

In the first of the secondary objectives, mcOPA GMTs measured one month after vaccination with 20vPnC were compared to one month after vaccination with 13vPnC/PPSV23 vaccines. The results indicated that although the mcOPA GMTs for the thirteen shared serotypes were lower in the 20vPnC vaccinated subjects compared to 13vPnC/PPSV23 vaccinated subjects, the 95% CIs for mcOPA GMTs overlapped between the vaccine groups. For the seven additional serotypes, other than serotype 8, mcOPA titers were higher in the remaining six serotypes in 20vPnC vaccinated subjects compared to 13vPnC vaccinated subjects. The mcOPA GMTs in subjects who received saline one month after the initial 20vPnC vaccination were slightly lower one month after the saline injection compared to the titers measured one month after 20vPnC vaccination. Analysis of mcOPA titers by assessing the GMFR before and one month after vaccination as exploratory objective revealed a profile similar to GMT evaluation between the two groups for the thirteen shared serotypes and for the seven additional serotypes. Similarly, the proportion of subjects with mcOPA titers  $\geq$  LLOQ at one month after the vaccination were higher in 13vPnC/PPSV23 vaccinees compared to those vaccinated with 20vPnC although the 95% CIs for mcOPA GMTs overlapped between the vaccine groups. Once again, serotype 8 had lower mcOPA titers  $\geq$  LLOQ at one month after the vaccination among the seven additional serotypes in 20vPnC group compared to subjects who received 13vPnC/PPSV23 vaccines. Finally, the profile of response for all 20 serotypes was the same as the mcOPA GMT analysis between the two groups when the proportions of subjects achieving  $\geq$  2-fold and  $\geq$  4-fold rise in mcOPA titers were analyzed.

The comparisons reported for mcOPA GMTs between the two groups were also made for IgG antibody responses against the 20 vaccine serotypes one month after vaccination. The conclusions of the IgG GMCs analysis were in support of the conclusions made in the mcOPA GMT analysis.

Long term persistence of immune response was assessed by measuring mcOPA titers and IgG antibody levels twelve months after the first vaccination. Both assays indicated that the functional immune responses and IgG antibody responses against vaccine serotypes declined from their one month after the initial vaccination levels for the subjects in both the groups. Despite the decline, both the assays indicated that the levels remained substantially higher than the levels recorded prior to immunization in both the groups. Both the mcOPA titer analysis and IgG antibody analysis indicated that the immune response profile observed at the post 1-month time-point against the individual serotypes was preserved at the 12-month time point. That is, the responses against the thirteen serotypes were lower in the 20vPnC immunized group compared to 13vPnC/PPSV23 group and responses to six of the seven additional serotypes were higher in the 20vPnC immunized group compared to 13vPnC/PPSV23 group. Response to serotype 8 remained lower in the subjects who received 20vPnC than the groups who received 13vPnC/PPSV23 vaccines.

### **Phase 1 studies**

Immune responses assessed in the two phase 1b studies indicated that the 20vPnC vaccine elicited increased functional and IgG antibody responses against the 20 serotypes.

**B7471001 (Immunogenicity of 20vPnC in adults 18 to 49 years old):** In study B7471001, in addition to safety, immunogenicity was evaluated in adult subjects 18 to 49 years of age who received 20vPnC or tetanus, diphtheria, pertussis (Tdap) vaccines. Immune responses were evaluated as secondary and exploratory objectives of the study. Blood samples were analyzed for immunogenicity, prior to and one month after the first vaccinations. Functional antibodies and IgG antibody concentrations against the 20 pneumococcal serotypes were assessed by mcOPA and (b) (4), respectively. The following secondary and exploratory immunogenicity endpoints were assessed:

#### *Secondary Endpoints*

- To describe pneumococcal serotype-specific mcOPA GMTs measured one month after vaccination.
- To describe pneumococcal serotype-specific mcOPA GMFRs measured from before vaccination to one month after vaccination.

#### *Exploratory Endpoints*

- To describe the proportion of subjects with pneumococcal serotype-specific mcOPA titers  $\geq$  LLOQ measured one month after vaccination.
- To describe pneumococcal serotype-specific IgG GMCs measured one month after vaccination.



- To describe pneumococcal serotype-specific IgG GMFRs measured from before vaccination to one month after vaccination.

The group vaccinated with 20vPnC elicited increased mcOPA titers for all 20 serotypes one month after the vaccination compared to prior to vaccination. There was no overlap in 95% CI between pre-immune and post one-month mcOPA GMTs. Subjects in control group (Tdap vaccinated) did not elicit an increase in mcOPA titers compared to pre-immune titers. Similarly, mcOPA GMFRs were numerically higher for all 20 serotypes in the 20vPnC group than in the Tdap group. The results in the exploratory endpoints also indicated that 20vPnC vaccine elicited immune response against all 20 serotypes as assessed by mcOPA titers  $\geq$  LLOQ, IgG GMCs, and IgG GMFRs one month after vaccination.

**B7471005 (Immunogenicity of 20vPnC and c7vPnC in adults 18 to 49 years old):** In study B7471005, in addition to safety, immunogenicity was evaluated in adult subjects 18 to 49 years of age who received 20vPnC, a complementary pneumococcal vaccine composed of the seven new serotypes in 20vPnC only (c7vPnC) or 13vPnC. Immune responses were evaluated as secondary and exploratory objectives of the study. Blood samples were analyzed for immunogenicity prior to and one month after the first vaccinations. Functional antibodies and IgG antibody concentrations against the 20 pneumococcal serotypes were assessed by mcOPA and (b) (4), respectively. The following secondary and exploratory immunogenicity endpoints were assessed:

#### *Secondary Endpoints*

- To describe pneumococcal serotype-specific mcOPA GMTs measured one month after vaccination.

#### *Exploratory Endpoints*

- To describe pneumococcal serotype-specific mcOPA GMFRs measured from before vaccination to one month after vaccination.
- To describe pneumococcal serotype-specific IgG GMCs measured one month after vaccination.
- To describe pneumococcal serotype-specific IgG GMFRs measured from before vaccination to one month after vaccination.

Both the mcOPA and (b) (4) assays indicated that the group vaccinated with 20vPnC elicited increased mcOPA titers and IgG antibody concentrations for all 20 serotypes one month after vaccination compared to prior to vaccination. There was no overlap in 95% CI between pre-immune and post 1-month mcOPA GMTs and IgG GMCs. Subjects in c7vPnC groups induced mcOPA titers and IgG antibody concentrations against the seven additional serotypes which were comparable to those induced by 20vPnC. As expected, there was no change in the mcOPA titers and IgG antibody concentrations against the thirteen common serotypes in the subjects who received the c7vPnC vaccine. The mcOPA titers and IgG antibody concentrations against the thirteen common serotypes were slightly higher in the 13vPnC groups compared to 20vPnC. The mcOPA GMFRs and IgG GMFRs for the thirteen serotypes were also

slightly higher in the 13vPnC group than the 20vPnC group. The mcOPA GMFRs and IgG GMFRs in the subjects in c7vPnC group and the 20vPnC groups were comparable.

## **Serology Assays**

### **Information request (IR-1, -2, -4, -5, -9) letters sent to Pfizer during the review of serology assay files**

The following IR letters were sent during the review of clinical serology of the BLA submission.

**IR-1 letter sent on 07 December 2020:** Initial review of the mcOPA validation documents resulted in an IR, which was sent on 07 December 2020 to request information and missing files regarding serology assays used to measure vaccine responses in immunized subjects. This IR included clarification of the mcOPA standard operating procedure (SOP) used for the validation and testing of clinical samples. The sponsor responded to this IR in BLA 125731/0.5 (12 December 2020) indicating that the SOP VR-TM-10184 was used to validate and test the seven additional serotypes. The validation and testing of mcOPA for seven additional serotypes were done at Pfizer's Pearl River, NY facility. The validation of the thirteen common serotypes was done at Pfizer's Pearl River, NY facility as part of 13vPnC submission using SOP VR-TM-10036. The SOP VR-TM-10036 was subsequently transferred to (b) (4) and were run under (b) (4) version of VR-TM-10036 (VR-TM-10036(b) (4) for the thirteen common serotypes in subjects vaccinated with 20vPnC.

The IR letter also included a request for missing files referenced in the mcOPA validation documents for the seven additional serotypes submitted to BLA 125731/0.5. Pfizer submitted these documents to BLA 125731/0.5. The applicant's response is adequate.

**IR-2 letter sent on 19 January 2021:** Further review of the mcOPA validation files indicated that files referenced in serotype 15C mcOPA validation documents were also not accessible. These documents were requested in an IR letter communicated to Pfizer on 19 January 2021. Pfizer submitted them to BLA 125731/0.9. The applicant's response is adequate.

**IR-4 letter sent on 03 February 2021:** Data supporting the performance of Quality Control sera (QCS) used in the analysis of the thirteen common serotypes (SOP VR-TM-10036) and the seven additional serotypes (SOP VR-TM-10184) from the time of assay validation until the completion of studies submitted to this BLA were requested. In the same IR, the document VR-SOP-LC-11076 (Procedure for Review of Streptococcus pneumoniae (b) (4) Microcolony OPA data) referenced in SOP VR-TM-10184 was also requested. This document outlines the calculation of mcOPA titers. Pfizer submitted the QCS performance data for SOP VR-TM-10036 and SOP VR-TM-10184 as well as the document VR-SOP-LC-11076 to BLA 125731/0.15. The applicant's response is adequate.

**IR-5 letter sent on 16 February 2021:** The sponsor used (b) (4) assay to measure IgG antibody responses to vaccine serotypes in Phase 1 (B7471001), Phase 1b (B7471005), and Phase 2 (B7471002) studies as exploratory endpoints. Although the SOP and validation reports for (b) (4) were reviewed during the IND phase (IND 11673), they were not submitted to the BLA. In an IR letter sent on 16 February 2021, the sponsor was asked to submit the SOP and validation data for (b) (4). Also, the sponsor was reminded during the IND review that (b) (4) cannot be used to assess fold-increase in IgG antibody responses because the validation data indicated that (b) (4) underestimates sample value relative to ELISA at the low end of the assay range. The sponsor responded to CBER IR in BLA 126731/16 (02 February 2021). In their response, the sponsor provided assay SOP, validation report for the 13 PCV13 serotypes, qualification data for the 7-additional serotypes, and the report with an assessment of the standard curve bias for the (b) (4) using historical data. The applicant's response is adequate.

**IR-9 letter sent on 08 April 2021:** In amendment 8 (12 March 2021), Pfizer submitted protocol B74771015 in which they outlined a phase 4 real-world study to evaluate the effectiveness of 20vPnC to prevent vaccine-type (VT) radiologically-confirmed community-acquired pneumonia (RAD+CAP). In this study, Pfizer plans to identify and serotype the pneumococcal bacteria causing the RAD+CAP using urine antigen detection (UAD) assay. Pfizer indicated that (b) (4) UAD assays will be used to detect the (b) (4). Pfizer indicated that in addition to the 20 serotypes in 20vPnC, the UADs are capable of detecting additional cross-reactive serotypes. The (b) (4)

(cross-reactive serotypes are indicated after the slash). In the IR letter, the sponsor was asked to submit the validation reports and data supporting the intended use of the assays prior to analyzing the Phase 4 study samples. In amendment 31 (21 April 2021), the sponsor responded by indicating that they commit the submitting the validation reports and the data supporting the intended use of the assays prior to analyzing samples from the Phase 4 study B7471015. The sponsor's response is adequate.

The second comment of the IR letter was about the (b) (4) assay that will be used to distinguish serotype (b) (4) in the bacterial cultures isolated from clinical samples. The sponsor was asked to submit product specifications documenting the ability of the assay to distinguish the indicated serotypes. In their response submitted to amendment 31, Pfizer indicated that the (b) (4) assays will be conducted by (b) (4)

The laboratory will use (b) (4) method and antisera from (b) (4), which is registered at the U.S. FDA with Owner Operator Number: (b) (4). According to Pfizer, (b) (4) are listed as either FDA (b) (4) exempt medical devices. A review of the antisera by (b) (4) indicated the sera

are capable of distinguishing cultured serotype (b) (4). The sponsor's response is adequate.

mcOPA performed at (b) (4) for the thirteen common serotypes (SOP VR-TM-10036 (b) (4))




Efficacy for all thirteen common serotypes in 20vPnC vaccinated subjects were evaluated at (b) (4) using mcOPA as described in SOP VR-TM-10036 (b) (4). The mcOPA performed at (b) (4) for 13vPnC serotypes was initially developed and validated at Pfizer (Pearl River, NY). This assay was first reviewed by CBER during the evaluation of BLA 125324/262 (13vPnC adults ≥ 50 years indication) (01 December 2011). The assay was subsequently transferred to (b) (4) and the transferred assay was reviewed by CBER as part of BLA 125324/933 (04 December 2013), BLA 125324/934 (04 December 2013) and BLA 125324/950 (19 December 2013) and BLA 125324/1373 (08 April 2016). Stability of assay performance from the time of validation (2009) until 2013 was reviewed under BLA 125324/933. In an IR (#4) sent to Pfizer on 03 February 2021, the applicant was asked to provide data supporting the stability of the assay after the testing of clinical samples in BLA 125423/933 until the end of the testing of the three clinical studies submitted to this BLA. Pfizer submitted QCS and proficiency panel testing data for the mcOPA assay used to measure titers for the thirteen common serotypes. According to the mcOPA SOP, each run includes (b) (4) titer QCS, both of which have specification limits that are used as part of system suitability criteria to determine the acceptability of assays. Measurement of QCS titers outside the specifications requires the repeat of the assay. Pfizer submitted graphs showing the titers of QCS sera from 01 January 2013 until 01 October 2020. The graph also showed the measurements inside and outside specification limits of QCS for the thirteen common serotypes. The data indicated that the number of titers outside the specifications varied depending on the serotype and the QCS. Serotypes (b) (4) had the most QCS with titers outside the specifications over time, while the performance of serotypes (b) (4) were the most stable with limited QCS manifesting titers outside the specifications. Pfizer also submitted graphs with results from proficiency panel testing during the February 2010 to March 2020 period. These graphs indicated stable performance of the assay, including the time period when the three phase 3 clinical study samples were tested.

#### **mcOPA performed at Pfizer for the seven non-13vPnC serotypes (SOP VR-TM-10184)**


The document VR-TM-10184 (Microcolony Pneumococcal Opsonophagocytic Assay for the Detection of Antibodies to *Streptococcus pneumoniae* in Serum Samples in (b) (4)) outlines the SOP for the mcOPA used to evaluate the seven additional serotypes. The principle of mcOPA is the killing of pneumococcal bacteria by phagocytic cells. Phagocytic elimination of bacteria correlates with the concentration of functional antibodies directed against the capsular polysaccharide. Bacteria-bound antibodies interact with complement which in turn leads to the opsonization of bacteria. In the experimental set up used by Pfizer, baby rabbit serum (BRC) is added as complement source. Human monocytic cell line HL-60 cells

are used as the phagocytic cells. The mcOPA antibody titer is the reciprocal of the serum dilution resulting in 50% reduction in the number of bacterial colonies when compared to the bacteria-effector cell-complement control wells that do not contain serum (defined as the background (b) (4)). The mcOPA is designed to measure the OPA of (b) (4) at (b) (4) titration. Sera were serially diluted at (b) (4) dilution until (b) (4) dilution. Specimens with (b) (4) were retested after (b) (4) of the test serum. Specimens that failed to kill 50% or more of the target bacteria when tested at a (b) (4) dilution were reported to have a mcOPA titer of (b) (4) of the lowest dilution tested.

According to the mcOPA SOP, an assay run was conducted in a (b) (4)





(b) (4)



Assay system suitability criteria were used to accept, repeat, or reject the runs. Among the system suitability criteria, QCS titers had to be within their prespecified limits. QCS titers were also accumulated to evaluate the assay performance stability over time.

**Calculation of mcOPA titers:** Serum mcOPA titers were calculated by (b) (4)






### mcOPA Validation

The following validation reports were submitted.

- VR-MVP-10065, The Method Validation of the (b) (4) Opsonophagocytic Assay for *Streptococcus pneumoniae* Serotypes 8, 10A, 11A, 12F, 15B, 15C, 22F, and 33F.
- VR-MVR-10064, Method Validation of the (b) (4) Opsonophagocytic Assay for *Streptococcus pneumoniae* Serotype 8A.
- VR-MVR-10065, Method Validation of the (b) (4) Opsonophagocytic Assay for *Streptococcus pneumoniae* Serotype 10A.
- VR-MVR-10066, Method Validation of the (b) (4) Opsonophagocytic Assay for *Streptococcus pneumoniae* Serotype 11A.
- VR-VTR-10654, Range Extension for the (b) (4) Opsonophagocytic Assay for *Streptococcus pneumoniae* Serotype 11A.
- VR-MVR-10067, Method Validation of the (b) (4) Opsonophagocytic Assay for *Streptococcus pneumoniae* Serotype 12F.
- VR-MVR-10068, Method Validation of the (b) (4) Opsonophagocytic Assay for *Streptococcus pneumoniae* Serotype 15B.
- VR-VTR-10597, Range Extension for the (b) (4) Opsonophagocytic Assay for *Streptococcus pneumoniae* Serotype 15B.

- VR-MVR-10071, Method Validation of the (b) (4) Opsonophagocytic Assay for *Streptococcus pneumoniae* Serotype 15C.
- VR-MVR-10069, Method Validation of the (b) (4) Opsonophagocytic Assay for *Streptococcus pneumoniae* Serotype 22F.
- VR-MVR-10070, Method Validation of the (b) (4) Opsonophagocytic Assay for *Streptococcus pneumoniae* Serotype 33F.
- VR-VTR-10293, Assay Specificity of Pneumococcal Microcolony Opsonophagocytic Assays for Next Generation *Streptococcus pneumoniae* Serotypes 8, 10A, 11A, 12F, 15B, 22F and 33F.
- VR-VTR-10558, Assay Specificity of Pneumococcal Microcolony Opsonophagocytic Assay for *Streptococcus pneumoniae* Serotype 15C.


(b) (4)



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



(b) (4)



#### **Stability of mcOPA performance assays over time**

**In an IR (#4) communicated on 03 February 2021**, Pfizer was asked to submit data supporting the stability of mcOPA performed at Pfizer (Pearl River, NY) facility for the measurement of titers against the seven additional serotypes. Pfizer submitted graphs depicting the QCS performance from the time of validation (01 July 2019) until the end of the completion of the three phase 3 clinical studies (01 June 2020) submitted to this BLA. These data indicated stable performance of the mcOPA.

#### **Measurement of serum IgG antibodies against pneumococcal polysaccharides in**

(b) (4)



(b) (4)

**(b) (4) validation report (VR-MVR-10025):**

For the validation of (b) (4) the sponsor evaluated assay accuracy, dilutional linearity, precision, assay range as well as the assay LLOQ and ULOQ.

(b) (4)

(b) (4)

(b) (4) validation report (VR-MPQ-10053):

(b) (4)

### **Animal immunogenicity studies**

Animal immunogenicity studies were conducted with c7vPnC as well as with the 20vPnC. These studies were conducted as part of antigenicity studies and repeat toxicity studies. These studies were submitted under pane 4, (Nonclinical Study Reports) as Pharmacology and Toxicology studies. Vaccine responses were assessed by measuring serum opsonophagocytic activity against serotypes of pneumococcal bacteria included in the 20vPnC using mcOPA. Also, serum IgG antibody responses was measured using (b) (4).

The mcOPA used for animal studies was similar to the mcOPA used in the evaluation of clinical samples. Titrated sera were incubated with the bacteria. Baby rabbit serum was used as complement and HL-60 cells were used as phagocytic cells. As in human mcOPA, the titer of serum eliciting 50% killing was recorded as OPA titer for that serum.

The (b) (4) was performed as (b) (4) format. As in human (b) (4) pneumococcal capsular polysaccharides were individually conjugated to (b) (4)

(b) (4)

### **Pharmacology studies:**

As part of Pharmacology studies, mice, rats, and rabbits were immunized. Mice were immunized to compare the immunogenicity of serotype 33F conjugates prepared according to (b) (4) methods. Mice were immunized twice on day 0 and on week 3. Serum mcOPA titers were analyzed on week 4 serum. The (b) (4) method was selected for the conjugation of 33F in 20vPnC because (b) (4). Another group of mice were immunized with c7vPnC twice given at 0.1 µg, 0.01 µg, or 0.001 µg doses three weeks apart. Serum mcOPA analysis demonstrated a concentration dependent increase in titers for all seven serotypes.

Rats were also immunized with c7vPnC containing 4.4 µg/mL of each serotype three times (day 0, weeks 3 and 6). All seven serotypes were immunogenic as evidenced by substantially increased IgG and mcOPA titers eight weeks after the first dose.

Rabbits were immunized with the clinical formulations of 20vPnC at weeks 0 and 2. Weeks 0 and 4 sera were evaluated in (b) (4) and mcOPA assays. 20vPnC elicited substantially increased immune response against all 20 serotypes.

### **Toxicology studies:**

Toxicology studies were conducted with a (b) (4)-valent PnC containing capsular polysaccharide serotypes (b) (4) and with 20vPnC. Five groups of rabbits were included in the study. Group 1 (Saline Control) received sterile saline for injection. Group 2 (Adjuvant Control) received (b) (4) succinate buffer and (b) (4) NaCl, at (b) (4) Polysorbate 80 and (b) (4) aluminum as AlPO<sub>4</sub>. Group 3 received (b) (4) at twice the maximum anticipated clinical dose in two injections per dosing day. Group 4 received 20vPnC at the maximum anticipated clinical dose. Group 5 received 20vPnC at twice the maximum anticipated clinical dose in two injections per dosing day. Each animal received a total of 5 doses over the course of 59 days. Doses were given by intramuscular injection once every 2 weeks on Days 1, 15, 29, 43 and 57. Two days after the last dose (Day 59), the first five male and female animals per group, in ascending animal order, were euthanized. On Day 87, the remaining animals were euthanized. Serum IgG antibody levels against vaccine serotypes were measured on study days, 8, 15, 59, and 87 after vaccination using (b) (4). The data indicated that both the vaccines induced robust IgG antibody responses against vaccine serotypes compared to rabbits immunized with the adjuvant only.