

CBER CMC BLA Review Memorandum

BLA STN 125814

Pneumococcal 21-valent Conjugate Vaccine (V116)

CAPVAXIVE

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VACCINES RESEARCH AND REVIEW**

1. **BLA#:** STN 125814

2. **APPLICANT NAME AND LICENSE NUMBER:**

Merck Sharp & Dohme LLC, 0002

3. **PRODUCT NAME/PRODUCT TYPE**

Pneumococcal 21-valent Conjugate Vaccine (V116)
CAPVAXIVE

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

- a. Pharmacological category: Vaccine
- b. Dosage form: Solution for injection
- c. Strength/Potency: Each 0.5-mL dose contains a total of 84 µg Pneumococcal polysaccharide antigens (4 µg each of serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, deOAc15B, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F and 35B) individually conjugated to CRM197. Each dose (0.5 mL) contains approximately 65 µg CRM197 carrier protein.
- d. Route of Administration: Intramuscular injection
- e. Indication(s): Active immunization for the prevention of invasive disease caused by *Streptococcus pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B in adults 18 years of age and older. It is also indicated for active immunization for the prevention of pneumonia caused by *S. pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B in adults 18 years of age and older (under accelerated approval).

5. **MAJOR MILESTONES**

- a. Acknowledgement Letter: October 27, 2023
- b. First Committee Meeting: November 2, 2023
- c. Filing Meeting: November 30, 2023
- d. Mid-Cycle Meeting: January 18, 2024
- e. Late-Cycle Meeting: March 21, 2024
- f. Request for reference product designation received October 8, 2023. The CMC team recommends to grant the designation. CBER's reference product determination board had not yet met to discuss the application at the time of finalization of the CMC memo. If approved by the board, the product will be designated as a reference product and the associated exclusivity periods will be based on the date of first approval.
- g. PDUFA Action Due Date: June 17, 2024

6. **CMC/QUALITY REVIEW TEAM**

Reviewer/Affiliation	Section/Subject Matter
Shonoi A. Ming, OVR/DBPAP/LBP	Sections 1, 2 and 3 (and subsections within)/CMC
Jiro Sakai, OVR/DBPAP/LBP	Sections 4 and 5/serology assays

7. INTER-CENTER CONSULTS REQUESTED

Reviewer/Affiliation	Section/Topic	In agreement with consult recommendations (Yes/No)
None	NA	NA

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
October 18, 2023	STN 125814/0	Original submission
November 30, 2023	STN 125814/0.4	CMC stability data
December 18, 2023	STN 125814/0.6	Response to IR sent December 7, 2023 (comments 1–4)
January 29, 2024	STN 125814/0.9	Submitted Comparability Protocols for new reference standards per commitment made in amendment 6 (comment 3) above.
February 8, 2024	STN 125814/0.10	Response to IR sent on January 30, 2024, requesting executed batch records for DP, as well as extractables and leachables reports; response to IR sent on October 18, 2023, requesting updated MOPA and Pn-ECL validation reports
February 15, 2024	STN 125814/0.13	Response to February 1, 2024, IR regarding SSUAD and PAD assays for Merck's proposed clinical study for pneumococcal pneumonia
March 8, 2024	STN 125814/0.14	Response to February 1, 2024, IR regarding SSUAD and PAD assays for Merck's proposed future clinical study for pneumococcal pneumonia
March 13, 2024	STN 125814/0.15	Response to IR sent on March 11, 2024, requesting analysis of OPA responses to serotype 15B
March 29, 2024	STN125814/0.20	Response to IR sent on March 22, 2024
April 5, 2024	STN125814/0.22	Response to IR sent on March 28, 2024, regarding executed batch records and post-approval change management protocol

April 19, 2024	STN125814/0.25	Response to IR sent on April 12, 2024, regarding (b) (4) specifications, reference standards, and (b) (4) used in the Total Saccharide assay
April 25, 2024	STN 125814/0.26	Response to IRs sent on April 18, 2024, requesting additional information on validations of Saccharide Content and Conjugated Saccharide Content assays (IRs 6 and 7 only; defer IRs 1–5 to CMC Statistical Reviewer)
April 30, 2024	STN 125814/0.27	Response to IR sent on April 23, 2024, requesting assay stability data for MOPA and Pn-ECL assays
May 6, 2024	STN 125814/0.28	Response to IR sent on May 2, 2024, regarding future validation studies for (b) (4) assays; defer review to CMC Statistical Reviewer
May 8, 2024	STN 125814/0.29	Response to IR sent on May 3, 2024, regarding developmental data for SSUAD
May 30, 2024	STN 125814/0.33	Response to IR sent on May 29, 2024, regarding the milestones for SSUAD/PAD validation protocols and reports

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

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
DMF (b) (4)	(b) (4)	(b) (4) Glass Syringe	Yes	Authorization for FDA to review information pertaining to (b) (4) Glass Syringe
DMF (b) (4)	(b) (4)	Contract Manufacturing Facility	Yes	Authorization for FDA to reference the entirety of information within DMF

DMF (b) (4)	(b) (4)	Primary Packaging Material Syringes	Yes	Authorization for FDA to review information pertaining to (b) (4) glass syringe
DMF (b) (4)	(b) (4)	Plunger stopper	Yes	Authorization for FDA to review information pertaining to syringe plunger
DMF (b) (4)	(b) (4)	Rubber Compounds	Yes	Authorization for FDA to review information pertaining to Compound (b) (4) and to (b) (4) washing process/Depyrogenation process

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

Merck is seeking licensure of a 21-valent pneumococcal conjugate vaccine (V116) for active immunization for the prevention of invasive disease caused by *Streptococcus pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B in adults 18 years of age and older. It is also indicated for active immunization for the prevention of pneumonia caused by *S. pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B in adults 18 years of age and older (under accelerated approval). Active ingredients consist of 21 pneumococcal polysaccharides (PnPs) conjugated to diphtheria Cross Reactive Material (CRM197). The PnPs are derived from the capsules of *S. pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, deOAc15B (de-O-acetylated serotype 15B), 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F and 35B. Of the 21 PnPs serotypes, 14 serotypes are shared with the firm's other licensed pneumococcal vaccines, V110 (Pneumovax 23) and/or V114 (Vaxneuvance) and are referred to as legacy serotypes. The remaining PnPs serotypes 15A, 16F, 23A, 23B, 24F, 31, and 35B developed for V116 are referred to as novel serotypes.

Each PnPs is manufactured using a common manufacturing process with some variations to accommodate differences such as (b) (4) properties of the serotype PnPs. The PnPs are (b) (4). Serotype 15B is de-O-acetylated (b) (4). The CRM197 carrier protein is an inactivated form of the Diphtheria toxin recombinantly expressed in *Pseudomonas fluorescens*. The PnPs are activated via (b) (4)

The PnPs are produced at Merck's (b) (4) manufacturing site. The CRM197 carrier protein is produced at (b) (4). The monovalent (b) (4) conjugates (b) (4) are produced at the MSD (b) (4) site in (b) (4). The drug product (DP) is formulated and filled at the MSD (b) (4) site in (b) (4).

Release tests and in-process tests for the manufacture of V116 were developed and validated as appropriate for all intermediates, DSs, and DP. The testing panels adequately measure quality and safety and provide a baseline of physiochemical and biological attributes. Some release tests have been incorporated into the stability testing program for intermediates, DSs, and DP. Hold times have been established and are supported by validation data.

The PnPs are stored at (b) (4) in (b) (4). The proposed shelf life of PnPs ranges from (b) (4), depending on serotype. Merck provided adequate stability data to support a shelf life of up to (b) (4) for legacy serotypes. For novel serotypes 15A, 16F, 23A, and 35B they provided adequate data to support a shelf life of (b) (4). For novel serotypes 23B, 24F, and 21 they provided adequate data to support a shelf life of (b) (4). Stability data submitted for the CRM197 intermediate stored at (b) (4) in (b) (4) supports a shelf life of (b) (4). The (b) (4) are stored in (b) (4) at (b) (4). The proposed shelf life of the (b) (4) ranges from (b) (4), depending on serotype. The proposed shelf life for serotypes 7F and 19A is (b) (4). The proposed shelf life for serotypes 6A, 8, 9N, 10A, 11A, 12F, 15A, deOAc15B, 16F, 17F, 20A, 22F, 23A, and 33F is (b) (4), and for serotypes 53, 23B, 24F, 31, and 35B is (b) (4). The information submitted supports the proposed shelf-lives. The DP is stored as a suspension in prefilled syringes with a proposed shelf life of 18 months stored at 2–8°C which is supported by the information submitted to the file.

Antibody-mediated opsonophagocytic killing is the primary mechanism involved in protection from invasive pneumococcal disease. Therefore, the opsonophagocytic activity (OPA) assay is used to assess vaccine-induced functional antibody responses and clinical efficacy as the primary endpoint in Merck's Phase 3 clinical studies. IgG antibody levels are a secondary endpoint in these studies. At the request of Merck Research Laboratory, (b) (4) developed the multiplexed opsonophagocytosis assay (MOPA) and the pneumococcal electrochemiluminescence (Pn-ECL) assay to assess clinical samples for primary and secondary endpoints, respectively, to support the immunogenicity of V116. They validated MOPA in terms of ruggedness and precision, relative accuracy/dilutional linearity, analytical specificity, and matrix interference. (b) (4) also developed the (b) (4) assay to screen serum samples from clinical studies for (b) (4) prior to the evaluation of functional antibodies of serum samples in MOPA. They validated Pn-ECL in terms of precision, assay ruggedness, selectivity, specificity, and dilutional linearity. All assays are adequate for their intended uses to evaluate primary and secondary

clinical endpoints, and data support that the assays were stable throughout the clinical testing period.

We recommend approval of STN 125814/0.

B. RECOMMENDATION

I. APPROVAL

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

DS and DP Manufacturing Facilities

Site Name and Address	Responsibility
(b) (4)	<ul style="list-style-type: none"> ▪ PnPs Master and working cell bank manufacture ▪ CRM197 working cell bank manufacture
Merck Sharp & Dohme LLC (b) (4)	<ul style="list-style-type: none"> ▪ PnPs and CRM197 master and working cell bank manufacture, (b) (4) ▪ PnPs master cell bank (b) (4) ▪ Pneumococcal polysaccharide (b) (4) manufacture, (b) (4) ▪ Combination Product Assembly ▪ Labeling and secondary packaging ▪ Finished product release site
(b) (4)	<ul style="list-style-type: none"> ▪ PnPs and CRM197 master and working cell bank storage
(b) (4)	<ul style="list-style-type: none"> ▪ CRM197 Working cell bank (b) (4) ▪ CRM197 Working and Master cell bank storage
(b) (4)	<ul style="list-style-type: none"> ▪ CRM197 manufacture, (b) (4)
(b) (4)	<ul style="list-style-type: none"> ▪ CRM197 release testing
(b) (4)	<ul style="list-style-type: none"> ▪ MBC manufacture, (b) (4)

Site Name and Address	Responsibility
Merck Sharp & Dohme LLC (b) (4)	<ul style="list-style-type: none"> ▪ (b) (4)
MSD (b) (4)	<ul style="list-style-type: none"> ▪ Drug Product Release and Stability Test Site (Physical-Chemical, Biological and Syringe Functionality)
MSD (b) (4)	<ul style="list-style-type: none"> ▪ Drug Product Manufacturing and Primary Packaging ▪ Drug Product Release and Stability Test Site (Physical-Chemical, Biological, Microbiological and Syringe Functionality)
(b) (4)	<ul style="list-style-type: none"> ▪ Drug Product Stability Test Site (Syringe Functionality and Container Closure Integrity)
(b) (4)	<ul style="list-style-type: none"> ▪ Drug Product Release and Stability Test Site (Conjugated Saccharide Content)
Merck Sharp & Dohme LLC (b) (4)	<ul style="list-style-type: none"> ▪ Combination Product Assembly ▪ Labeling and secondary packaging ▪ Finished product release site

PnPs, pneumococcal polysaccharide Drug Substance Intermediate; (b) (4)
Drug Substance.

Comparability Protocols

The following comparability protocols are included in the BLA:

- Post-approval change management protocol for reference standards for drug product (DP): This comparability protocol (CP) describes the plan for the introduction of new DP (b) (4). The CP also includes the plan for the shelf-life extension of the SRS. Merck will report the (b) (4) of shelf-life of the SRS and the introduction of (b) (4) in an annual report. The introduction of (b) (4) will be reported in a CBE-30.
- Post-approval change management protocol for reference standards for drug substance (DS): This CP describes the plan for the introduction of new DS reference standards used to determine (b) (4). The CP also includes the plan for (b) (4) of shelf life for the reference standard. Merck will report the (b) (4) of shelf-life and introduction of new reference standard in an annual report.

II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Shonoi Ming, PhD Biologist CBER/OVRR/DBPAP/LBP	Concur	
Jiro Sakai, PhD Biologist CBER/OVRR/DBPAP/LBP	Concur	
Willie F. Vann, PhD Chief CBER/OVRR/DBPAP/LBP	Concur	
Jay E. Slater, MD Director CBER/OVRR/DBPAP	Concur	

Review of CTD
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Module 3

Reviewed by SM

3.2.S DRUG SUBSTANCE

(b) (4) [Redacted]

(b) (4) [Redacted]

[Redacted]

[Redacted]

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

(b) (4)

3.2.P DRUG PRODUCT

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

The V116 DP is prepared by combining the 21 MBC DS. Each 0.5-mL dose of the DP contains 4 µg of each PnPs conjugated to CRM197. Additional components of the DP include 1.55 mg/mL histidine, 0.5 mg/mL PS-20, and 4.49 mg/mL NaCl. The DP is supplied as a prefilled syringe (PFS) and is therefore considered a combination product. The components of the syringe are:

- A syringe barrel assembly consisting of:
 - A 1.5-mL Type ^{(b) (4)} glass syringe barrel with Luer Lock adaptor, round flange, siliconized, and without graduation marks
 - A plastic tip cap with elastomeric closure
- Plunger stopper
- Plunger rod

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

There are 21 drug substances, each comprising one of 21 PnPs (serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, deOAc15B, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B) individually conjugated to CRM197. (b) (4)

3.2.P.2.1.2 Excipients

A list of DP components, including the excipients and the purpose for their use in the DP, is provided in Table 2 of section 3.2.P.2.1 COMPONENTS OF THE DRUG PRODUCT and also listed in section 3.2.P.1 of this memo, above. The excipients include NaCl, PS-20, L-histidine, and WFI. NaCl serves to produce an isotonic (150 mM) environment which reduces injection pain. PS-20 is a surfactant that is used as

(b) (4). Histidine buffer is used to (b) (4)

(b) (4) of the DP during manufacturing and storage. WFI is used to prepare the solutions and buffers.

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

V116 is a liquid DP filled in 1.5-mL syringes. Merck used their prior knowledge and experience with V114 (their commercially approved 15-valent pneumococcal conjugate vaccine) in V116 development. The following are differences between V116 and V114:

- V114 contains aluminum phosphate as an adjuvant while V116 does not contain adjuvant.
- The surfactant PS-20 concentration is lower in V116 at 1mg/mL vs 2 mg/mL in V114. The lower concentration of PS-20 for V116 was selected based on the results from a formulation development study to determine the optimum concentration of PS-20 required to maintain the stability of the DP. The study analyzed the saccharide content of a representative subset of serotypes (8, 9N, 10A, 16F, 19A, 20A and 33F) with five PS-20 concentrations ((b) (4)) stored for (b) (4) . All formulations were stable through (b) (4) except at the (b) (4) PS-20. Therefore, Merck selected (b) (4) PS-20 as the DP formulation target with an acceptance criterion of (b) (4) PS-20 to (b) (4) PS-20.
- The DS target concentration is higher for V116 than in V114 (b) (4) .

The formulation of V116 (i.e., 21 MBC in 3.1 mg/mL L-histidine buffer, and (b) (4) mg/mL NaCl at 1.0 mL dose) has remained the same throughout development, with the exception of a DS concentration increase from 84 µg/mL to 168 µg/mL to allow for administration of a 0.5-mL dose. A 0.5-mL dose was selected for Phase 3 and PPQ batches to align with the injection volume of Merck's related products.

(b) (4)

(b) (4)

[Redacted text block]

[Redacted text block]

The DP formulation process is similar for clinical and commercial formulations. The following are the differences between the formulation process for the clinical and commercial formulations:

- The formulation size – The phase 3 clinical trial formulation batch size was (b) (4) while the PPQ/commercial formulation has (b) (4). The reason for the difference in batch sizes is to provide process flexibility and to meet future demand.

- Formulation suite – The phase 3 material was produced in the syringe formulation suite at (b) (4) while the commercial batches are manufactured in the vial and syringe suite at (b) (4).
- (b) (4) put-away time – (b) (4) for phase 3 material and (b) (4) for the commercial process. The change was made to reflect manufacturing process capability.
- Sterile filtration – (b) (4) filter versus a (b) (4) filter. While the (b) (4) filters were used for phase 3 due to supply issues, Merck indicated that the (b) (4) filter is the ideal size and thus is used for the commercial batches.
- Plunger stopper – Stoppers with target (b) (4) level of (b) (4) were used for the clinical trial while a combination of stoppers with a target (b) (4) level of (b) (4) and/or a reduced target (b) (4) level of (b) (4) are used in the commercial batches.
- Syringe barrel assembly – The (b) (4) barrels were used for the phase 3 material whereas (b) (4) and (b) (4) syringes were used for PPQ batches. The (b) (4) specifications for the (b) (4) syringes were tightened for visual inspection and attribute testing. However, the syringe barrel and components, dimensions, site of sterilization, and final packaging configuration for (b) (4) syringes remain the same as the (b) (4) syringe. PPQ batch (b) (4) used both (b) (4) and (b) (4) syringes. (b) (4) syringes were used in addition to the (b) (4) syringes for PPQ batches to provide an alternate source of syringes.

3.2.P.2.2.2 Overages

No overages were described.

3.2.P.2.2.3 Physicochemical and Biological Properties

The DP is composed of the 21 (b) (4) DS formulated with NaCl, PS-20, L-histidine, and WFI. There are no physicochemical or biological properties relevant to safety, performance, or manufacturability that set it apart from the drug substances.

3.2.P.2.3 Manufacturing Process Development

3.2.P.2.3.1 Drug Product

Table 1 of this section of the eCTD provides an overview of the V116 manufacturing history. Merck manufactured their early development pre-clinical batches, phase 1/2 clinical lot, and pilot-scale stability (PSS) batch (representative of Phase 3 formulation) at (b) (4). Phase 3 clinical trial lots, the primary stability study batch, and PPQ batches were manufactured at (b) (4), as will be the commercial product. The firm used DS manufactured at (b) (4) in the manufacture of DP produced at (b) (4), and DS manufactured at (b) (4) in the manufacture of DP produced at (b) (4). (b) (4) were used as the fill container for the early development pre-clinical batches. The applicant used PFS as the final fill container for all other DP batches manufactured at (b) (4). PFS was the final fill container for all DP batches manufactured at (b) (4).

The formulation process for DP has remained relatively unchanged throughout the DP development process with minor updates (see Table 5 of section 3.2.P.2.3.1). These changes are described under section 3.2.P.2.2.1, above.

Based on the differences between the Phase 3/PSS batches and PPQ batches there is no expected impact to product quality. There was no impact on saccharide content due to the processing differences for Phase 3, PSS, and PPQ batches (see table 6 of section 3.2.P.2.3.1).

Process Risk Assessment

Merck used a Process Hazard Analysis (PHA) methodology to identify all potential hazards, hazardous situations, and events that may cause potential harm to product quality, to rank the potential risk according to severity of the harm, the probability of the hazard to result in harm, and the ability to detect the hazard, hazardous situation, or harm. They completed risk scoring in line with ICH Q9 guidelines. The applicant identified 241 low risks and one medium risk; the medium risk was for potential bioburden contamination of the WFI point, which due to an operator error in sampling procedure could result in potential bioburden ingress and endotoxin proliferation. However, they did not implement any mitigating action due to low probability of occurrence with existing controls in place, such as loop qualification and the site's testing and monitoring program (see 3.2.A.1.3 CLEAN UTILITIES (b) (4)).

Merck also used PHA methodology in parameter classification for the final commercial DP manufacturing process. Parameters that have potential impact on CQA and a probability of occurrence greater than negligible were classified as Critical Process Parameters (CPP). Following completion of the assessment, the applicant implemented the identified CPPs identified in the control strategy shown in Section 3.2.P.3.3.1 DESCRIPTION OF MANUFACTURING PROCESS AND PROCESS CONTROLS. PHA scoring methodology is presented in Table 7 of 3.2.P.2.3.1.

Manufacturing Process Development Studies

Merck performed laboratory-scale studies at (b) (4), which include the following: (b) (4)

(b) (4)
They concluded that, for all studies, there was no impact on product quality.

The conjugated saccharide content for serotypes 15A, deOAc15B, 16F, 17F, 19A, 23A, 23B, 24F, and 35B in primary packaging show photosensitivity at (b) (4) levels (See Figure 13 of section 3.2.P.2.3.1). However, Merck concluded that there is no impact to the DP since under the manufacturing light conditions for the end-to-end DP process at MSD (b) (4), they did not observe an impact on conjugated saccharide. In addition, Merck states that they have existing light protection measures in place. With their release tests downstream of filling, any loss

due to light exposure would be detected prior to release; combined with the light conditions during manufacture, the risk to product quality is minimal. However, due to the observation of photosensitivity at (b) (4) levels on the conjugated saccharide content for serotypes 15A, deOAc15B, 16F, 17F, 19A, 23A, 23B, 24F, and 35B in the primary packaging, Merck has included on the carton label language to advise users to keep the container in the outer carton to protect from light.

Commercial-scale studies performed at the (b) (4) site included: PS-20 solution (b) (4), and batch downtime. Based on these studies Merck established the following:

- A minimum (b) (4) of (b) (4) for the PS-20 solution
- A minimum (b) (4) of (b) (4) through the syringe filling filtration manifold
- A DP target fill dose of (b) (4) and allowable range of (b) (4)
- A maximum down time of (b) (4)

The risk assessment, process development, and optimization studies support the conclusion that Merck has an appropriate formulation fill process in place.

3.2.P.2.3.2 Combination Product

Final combination product assembly consists of the addition of the plunger rod to the PFS. For the clinical trial material, the combination product assembly was performed manually. For the commercial assembly, an automated process was established. Table 1 of section 3.2.P.2.3.2 MANUFACTURING PROCESS DEVELOPMENT - COMBINATION PRODUCT lists the differences between the clinical and commercial assembly/packaging processes.

Process Risk Assessment

The combination product assembly steps were developed using process risk assessments with the goal to optimize the consistency of the assembled combination product. In addition, manufacturing process attributes were identified and evaluated as a part of the risk assessment (see Table 2 of section 3.2.P.2.3.2). In-process controls were established to ensure a robust assembly process (see Table 3 of section 3.2.P.2.3.2).

Photosensitivity

The PFS photostability was assessed using a representative plunger stopper and syringe barrel combination exposed to (b) (4) levels to support worst-case light exposure during packaging. Exposure to these lighting conditions had no impact to product quality.

Changes after combination product assembly and packaging qualification

The differences between the PPQ and commercial batches are provided in Table 4 of section 3.2.P.2.3.2. They include the following component differences:

- Syringe barrel: 1.5-mL Luer Lock adapter (LLA) (b) (4) for PPQ batches and 1.5-mL LLA (b) (4) for commercial batches. Merck justified the change because

specifications for the two types of syringes differ only for visual inspection and attribute testing.

- Plunger stopper: (b) (4) was used in manufacture of PPQ batches whereas (b) (4) are used for commercial batches. A (b) (4) stopper was introduced for use in addition to the (b) (4) to allow manufacturing flexibility.

3.2.P.2.3.3 (b) (4) AND (b) (4) Comparability

Merck used (b) (4) syringes in their V116 clinical trial program, but will use both (b) (4) and (b) (4) syringes for the commercial DP to reduce the risk of supply interruptions. Thus, Merck assessed the comparability of the (b) (4) syringe barrel assemblies and the (b) (4) syringe barrel assemblies.

The (b) (4) syringe has been approved for the use with other vaccines, including V110 and V114. Both syringe barrel assemblies consist of the syringe barrel with a LLA and a plastic tip cap with an elastomeric closure. A description of each assembly barrel is presented in Table 1 of section 3.2.P.2.3.3 MANUFACTURING PROCESS DEVELOPMENT – (b) (4) COMPARABILITY. The clinical trial lots used (b) (4) syringes while the commercial lots used (b) (4) syringes. The difference between the (b) (4) syringes is that the (b) (4) specifications for the (b) (4) syringes are tightened for visual inspection and attribute testing. Data obtained from stability studies, batch analyses, and validation of analytical procedure for container closure integrity demonstrate that the two syringes are comparable. In addition, the components of syringes are comparable.

3.2.P.2.3.4 Analytical Development

All methods remained consistent throughout development except the method for determining container closure integrity. The method was changed between Phase 1/2 batches and Phase 3/PSS/PPQ and commercial batches. For Phase 1/2, samples were analyzed by an (b) (4) method. For Phase 3/PSS/PPQ and commercial stability, container closure integrity was assessed by (b) (4).

3.2.P.2.4 Container Closure Development

The combination product consists of a PFS with the plunger rod. Merck receives from the vendor syringe barrels and barrels that are ready to use (syringes are assembled, both are sterilized by (b) (4)). The plunger rod does not have direct contact with the DP. Therefore, Merck does not consider it a primary packaging component. The applicant provided the following studies to demonstrate suitability of the container closure system for the DP:

Choice of Materials

Merck assessed the use of the PFS (either the (b) (4) syringe barrel assembly) using (b) (4) testing and (b) (4) standards. They performed a biocompatibility assessment to evaluate potential biological risk. The biocompatibility assessment per (b) (4)

included a review of the physical and chemical information, the materials of construction, and manufacturing process, along with a review of the biological safety information. The risk assessment found no materials that indicated a safety concern. The needle supplied where applicable, meets (b) (4) relevant requirements. The components of the PFS ((b) (4) syringe barrel assemblies and the (b) (4) plunger stopper) that are in contact with the DP meet the established (b) (4) Criteria.

Extractables Studies

The applicant performed an assessment of extractables to identify potential leachables for each component of the container closure system (i.e., syringe barrel, plunger stopper, and tip caps). The extractables studies involved (b) (4) followed by analysis of volatiles, semi-volatiles, and non-volatiles with (b) (4).

- (b) (4) **syringe barrels:**
 - No volatile, semi-volatile and non-volatile extractables were observed at levels greater than the reporting thresholds.
 - No metal extractables were observed at or above the (b) (4) permitted daily exposure levels.
(b) (4) was observed at (b) (4) /syringe.
- (b) (4) **syringe barrels:**
 - No volatile compounds were detected above the reporting threshold.
 - No non-volatile compounds were detected in any of the (b) (4). Several unknown compounds were detected in (b) (4) (between (b) (4) /syringe).
 - Several metals were observed above the analytical evaluation threshold (AET). However, the levels observed were below the permitted exposure levels.
(b) (4) was observed at (b) (4) /syringe.
- (b) (4) **plunger stopper:**
 - (b) (4) were observed above the AET in the volatile analysis.
 - No reportable extractables were observed above the AET from (b) (4). However, (b) (4) and some unknowns were observed above the AET in the semi- and nonvolatile analysis from (b) (4).
 - (b) (4) were observed above the AET.
No nitrosamines were detected.
- (b) (4) **tip cap:**
 - (b) (4) were observed above the AET in the volatiles analysis.
 - No semi- and non-volatile compounds were observed.
(b) (4) were observed.
- (b) (4) **tip cap:**

assembled, packaged, and then subjected to simulated shipping. All results met the break loose and glide force acceptance criteria of (b) (4).

Merck also assessed recoverable volume. All results met the acceptance criterion of 0.500 (b) (4) mL.

For a more detailed review of these factors please refer to the device reviewer's memo.

Container Closure Integrity (CCI)

The applicant performed container closure integrity testing to demonstrate the seal formed between the container closure components of the primary packaging can prevent leakage or ingress of external contaminants. All (b) (4) assessed samples of the syringe barrel assembly components from (b) (4) passed the test as no leaks were detected. For further details please refer to the DMPQ reviewer's memo.

Photostability

Merck performed photostability testing according to ICH Q1B requirements. The photosensitivity study assessed syringes in (b) (4) configurations (b) (4) (b) (4)). The results of the photostability studies for serotype (b) (4) showed a statistically significant change in Saccharide Content when exposed to light for the (b) (4) compared to the control. In addition, while the (b) (4) from (b) (4) syringes conformed to specifications for Appearance - Opalescence and (b) (4), the nude configuration for both syringes did not conform to specifications for Appearance - Degree of Coloration. Therefore, based on the results of this study Merck concluded that the labeled storage statement should include "protect from light."

Simulated Shipping

Merck performed functional testing on samples representative of the commercial product. The combination product samples were labeled, assembled, packaged, and subjected to simulated shipping conditions. For additional details please refer to section 3.2.P.3.5 PROCESS VALIDATION AND/OR EVALUATION, below.

Information Requests

On **January 30, 2024**, we sent two IRs asking Merck to provide the missing leachables/extractables reports for (b) (4) DP (Comment 3), respectively (see also section 3.2.S.6, above). Merck responded to our IRs in amendment 10 (STN125814/0.10, Sequence Number 0011). They provided in section 3.2.R the full leachables/extractables reports for the (b) (4) DP.

Below is a list of all the leachables/extractables report submitted with Merck's response:

- CEL-RPT-000254: Extractables Evaluation for the (b) (4)

- CEL-RPT-000668: Extractables and Leachables Evaluation for V116 Drug Product in (b) (4) Syringes
- Extractables Compounds Screening on (b) (4) Based on (b) (4) Protocol
- Extractables Compounds Screening on (b) (4) Based on (b) (4) Protocol
- Forced Extraction Study Report for (b) (4) and Closure
- CEL-RPT-000162 (b) (4) Standard Extraction Protocol

The provided reports included the raw data on compounds identified, the test methods used along with the Limit of Detection for each, and the level of each compound that was found. The response is acceptable.

3.2.P.2.5 Microbiological Attributes

The DP is sterile filtered and then filled using validated aseptic processing. Merck performs tests for sterility and endotoxin testing as part of routine product release. In addition, they also perform container closure integrity and sterility testing as part of stability monitoring.

3.2.P.2.6 Compatibility

The DP does not require reconstitution. Merck demonstrated the DP to be compatible with the syringe container closure system by compendial testing of the components, a biocompatibility assessment, and DP stability studies.

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

The DP developmental activities presented in this section are adequate. In addition, based on the (b) (4) testing, (b) (4) standards for prefilled syringes, extractables and leachables, container closure integrity, and photostability studies, the container closure system is suitable for the DP. I did not identify any deficiencies.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

Table 6. Drug Product Manufacturing and Testing Sites and Responsibilities

Site Name and Address	Responsibility	FEI# (DUNS#)
MSD (b) (4)	<ul style="list-style-type: none"> • Drug Product Release and Stability Test Site (Physical-Chemical, Biological and Syringe Functionality) 	(b) (4)

MSD (b) (4)	<ul style="list-style-type: none"> • Drug Product Manufacturing and Primary Packaging • Drug Product Release and Stability Test Site (Physical-Chemical, Biological, Microbiological and Syringe Functionality) 	(b) (4)
(b) (4)	<ul style="list-style-type: none"> • <p>The following analytical procedures and their validations were reviewed by the DBSQC: Identity, (b) (4), Endotoxin, (b) (4), and Bioburden. Please refer to the DBSQC review memos for details on these analytical procedures and their validations.</p>	(b) (4)
(b) (4)	<ul style="list-style-type: none"> • Drug Product Release and Stability Test Site (Conjugated Saccharide Content) 	(b) (4)
Merck Sharp & Dohme LLC (b) (4)	<ul style="list-style-type: none"> • Combination Product Assembly • Labeling and secondary packaging • Finished product release site 	(b) (4)
Merck Sharp & Dohme LLC (b) (4)	<ul style="list-style-type: none"> • Combination Product Assembly • Labeling and secondary packaging • Finished product release site 	(b) (4)

In Table 1 of section 3.2.P.3.1 MANUFACTURER(S) (also see Table 6 above), Merck has listed both (b) (4) as the manufacturing sites responsible for Drug Product Release and Stability testing. However, they did not indicate in the submission which release and stability tests are performed at each site. Therefore, we sent an IR to Merck on March 22, 2024, requesting that they provide list confirming location where the release and stability tests are performed. Merck responded to our request on March 29, 2024 (STN125814/0.20, Sequence Number 0021).

Information Request

On **March 22, 2024**, we sent the following information request to Merck. Merck responded to this request on March 29, 2024 (STN125814/0.20, Sequence Number 0021).

CBER Comment 3: In Table 1 of section 3.2.P.3.1 MANUFACTURER(S), you list (b) (4) as manufacturing sites responsible for Drug Product Release and Stability Testing. However, you have not indicated within your submission which release and stability tests are performed at each site. Because assays need to be

validated in each site that will perform routine testing, it is important to clearly define what tests are performed where and to provide documentation supporting the assay(s) is adequately validated at each site. To this end, please provide a list confirming the release and stability tests performed at each site. Please submit the respective assay validations and assay procedures. If they have been previously submitted, please state their location in the submission and include hyperlinks to the documents in your response.

Response: Merck has provided lists confirming the release and stability tests performed at each site. The DP release tests will be performed at (b) (4) and DP stability testing will be performed at (b) (4). In addition, they have submitted the respective assay validations and procedures for review (refer to sections 3.2.P.5.2 and 3.2.P.5.3 below). The response is acceptable.

3.2.P.3.2 Batch Formula

Merck has provided batch formulas for (b) (4) batch sizes. In the (b) (4) batch size there are (b) (4) of each PnPs and in the (b) (4) batch size there are (b) (4) of each PnPs. Each batch also contains the following additional components:

- Sodium chloride (b) (4)
- Polysorbate-20 (b) (4)
- L-histidine (b) (4)
- Water for injection (qQuantum sufficit (qs))

There are no overages. The quality of the additional components is assessed based on (b) (4). The PnPs quality is assessed based on internal specifications that are described in section 3.2.S.4.1 SPECIFICATION (MBC).

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

The information provided is acceptable as submitted.

3.2.P.3.3 Description of Manufacturing Process

Each batch of DP is assigned a (b) (4)-digit batch number that is generated automatically by the applicant's inventory management system. The DP batch date of manufacture is defined as the date of addition of the first MBC to the CB vessel.

The DP is manufactured by (b) (4)

Prior to filling, the pre-sterile syringes are decontaminated by (b) (4). The plunger stoppers are received on onsite pre-washed, (b) (4) and sterilized. The (b) (4) is sterile filtered into syringes and the plunger stopper set in place automatically. IPC testing for bioburden and endotoxin (b) (4), bioburden (b) (4) filtration, and (b) (4) test for the sterile filter are conducted (b) (4) filling the (b) (4) into the syringes. During filling the applicant confirms dose (b) (4) as a CPP. The filled syringes are 100% visually inspected by an automated inspection machine. Manual inspection by qualified inspectors can also be used to visually inspect the final filled containers in place of the automated machine. After inspection the syringes are stored in (b) (4) at 2–8°C in preparation for packaging and labeling.

An option for contingency filling is in place in the event of a filling line interruption (such as a filling line malfunction). In such a case, the remaining (b) (4) will be kept at (b) (4) and used in subsequent filling, which requires a new (b) (4) sanitation cycle and aseptic setup. This subsequent fill is assigned a new batch number.

The PFS are received from the DP manufacturing facility for assembly with the plunger rod. The combination product assembly is automated. The prefilled syringes are fed into the assembly and labeling machine and the plunger rod is threaded into the plunger stopper. IPC to confirm following are conducted (b) (4):

- (b) (4)

At the labeling step the batch number and the expiration date are printed on each label and applied to the unlabeled syringe. Each batch is assigned a (b) (4)

An IPC check using 100% visual verification is used to confirm the presence of printed batch related data on the label and presence of label on each syringe.

Upon completion of assembly and labeling of the syringes, but prior to placement into a carton with package insert, Merck conducts IPC tests to verify the following:

- (b) (4)

The cartons are placed into shipping containers and stored at 2–8 °C protected from light.

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

I found no deficiencies. The information submitted is acceptable.

3.2.P.3.4 Controls of Critical Steps and Intermediates

Formulation and Filling

Tests performed at release for the DP serve as a measure of product quality and manufacturing consistency. Table 1 of section 3.2.P.3.4.1 CONTROL OF CRITICAL STEPS AND INTERMEDIATES – FORMULATION AND FILL describes the IPC and CPP for DP manufacturing process. A series of IPC are in place for the (b) (4), DP formulation, inspection, and storage (see Figures 1 and 2 of 3.2.P.3.3.1 DESCRIPTION OF MANUFACTURING PROCESS AND PROCESS CONTROLS – FORMULATION AND FILL). These include (b) (4) testing where appropriate. Bioburden, endotoxin, and filter (b) (4) testing are performed (b) (4). The fill CPP is dose (b) (4), with an acceptance criterion of (b) (4).

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

I found no deficiencies. The information submitted is acceptable.

3.2.P.3.5 Process Validation and/or Evaluation

Single-Use Components

Merck has defined single-use DP PCMs as natural and synthetic polymers that are in contact with (b) (4), formulation process, and syringe filling paths. The PCMs are qualified by assessing the risk to patient safety and effect on product quality. The assessment entailed identifying potential leachables and extractables associated with the PCMs during the DP manufacturing.

Merck with first identified all the PCMs used in the DP manufacturing and grouped them based on material of construction, manufacturer, method of sterilization, and type of component. (b) (4) PCM groups were identified from which the applicant selected one representative from each group to be assessed. The representative was selected based on manufacturing process knowledge, largest surface area/volume ratio, and process conditions. They then assessed the (b) (4) representative PCMs and gave each an overall risk outcome (low, medium, or high) based on scoring for each risk factor (route of administration, proximity to final product, contact time, surface area/volume ratio; see Table 1 on page 2 of section 3.2.P.3.5.1 PROCESS VALIDATION AND OR EVALUATION – SINGLE-USE COMPONENTS for scoring values for low, medium, and high risk). The assessment did not identify any high-risk factor PCMs. However, the firm did identify (b) (4) medium-risk factor PCMs (see Table 2 on page 3 of 3.2.P.3.5.1).

Merck also reviewed the vendor documentation and prior extractables studies for each PCM. However, they did not perform additional leachable and extractables studies since they found the vendor documentation and previous data to be sufficient (they met biocompatibility specifications for (b) (4)). Furthermore, Merck has performed sorption and compatibility testing for (b) (4) on the medium-risk PCMs to confirm that there is no adsorption or absorption effects with DP at the (b) (4) stages in the manufacturing process and that the DP quality is not affected due to contact with these materials. Merck states that the results from the testing support the use of the medium-risk PCMs. Finally, a review of the vendor sterilization validation was conducted for the PCMs and confirmed that the materials met the acceptance criteria for sterilization assurance.

Therefore, based on the assessment, testing, and review of documentation described above, Merck has concluded that all the single-use PCMs used in the manufacture of DP are suitable for their intended use and are qualified.

Sterilization Filter

The sterilization filter validation met the following requirements:

(b) (4)

[Redacted text block]

(b) (4)

[Redacted text block]

[Redacted text block]

[Redacted text block]

(b) (4)

Shipping Qualification

Shipping qualification studies of the PFS and final packaged product were performed to demonstrate that the commercial packaging components will remain intact and maintain temperature integrity during transport. The studies included thermal and operational qualifications.

(b) (4)

The qualification of the TPS was conducted (b) (4).

Testing (b) (4) TPS is considered worst-case scenario since a product load preconditioned at 2–8°C would likely maintain temperature (b) (4). This TPS was able to maintain an internal temperature of 2–8°C in all conditions tested (Table 1 of section 3.2.P.3.5.4 PROCESS VALIDATION AND OR EVALUATION – SHIPPING QUALIFICATION).

Distribution qualification was performed using (b) (4)

Merck has provided a representative distribution qualification for unlabeled PFS and PFS finished product. The results of the visual inspections are presented in Tables 2–5 of section 3.2.P.3.5.4 PROCESS VALIDATION AND OR EVALUATION – SHIPPING QUALIFICATION. The maximum and minimum load results post-test visual inspection for the unlabeled PFS and finished PFS met the acceptance criteria. There were no critical, major, or minor defects observed.

The shipping qualification studies have demonstrated that the TPS can maintain the appropriate temperature during transport. In addition, the studies have demonstrated the shipping components will remain intact over a combination of (b) (4) transportation modalities.

Combination Product – (b) (4)

The PPQ studies performed at (b) (4) were conducted to support the assembly process of the plunger rod into the PFS to produce a combination product. The PFS assembly process is an existing process that is used for other vaccines. The PPQ studies consisted of (b) (4) distinct final assembly batches; Merck used PFS filled at the commercial DP manufacturing site and included (b) (4) syringe batches and (b) (4) syringe batch. One plunger rod supplier batch was used for all (b) (4) PPQ batches. In addition to IPC testing and release testing, the PPQ batches were subjected to functional testing. There were no deviations during the validations. All results met the pre-determined acceptance criteria.

Process Validation of DP Process

(b) (4) PPQ batches were manufactured consecutively in (b) (4) to demonstrate that all IPC, CPP, and CQA meet the pre-determined acceptance criteria. Batches were formulated at (b) (4) scale and filled into either (b) (4) syringes.

Hold Times

There were (b) (4) hold times ((b) (4) , and sterile filling time) executed during the PPQ study (see Table 2 on page 4 of section 3.2.P.3.5.2 PROCESS VALIDATION AND/OR EVALUATION-DRUG PRODUCT PROCESS VALIDATION).

(b) (4)

(b) (4)

Sterile Filling (b) (4) Hold Times

The sterile filling (b) (4) hold times were qualified by simulation using (b) (4) media and not repeated during the PPQ.

PPQ Hold Times

The PPQ hold times executed for (b) (4), sterile filling, (b) (4) were within the maximum demonstrated hold times for each. The (b) (4) storage time was validated during the PPQ where each batch was subjected to the maximum (b) (4) storage time of (b) (4).

PPQ CPP and IPC

The CPP for syringe filling dose (b) (4) was assessed for the (b) (4) PPQ batches and all met the acceptance criterion (target: (b) (4), range: (b) (4)). IPCs were evaluated as a part of the PPQ and met the acceptance criteria (see Tables 10 and 11 on page 7 and 8 of section 3.2.P.3.5.2).

PPQ CQA

All results from the PPQ met the release specifications (see Table 12 on pages 8–12 of section 3.2.P.3.5.2).

PPQ Sampling and Statistical Evaluation

Merck has provided a PPQ sampling plan for PPQ samples. The samples were taken at equal time points during the PPQ batch (see Table 13 of section 3.2.P.3.5.2). (b) (4) representative serotypes ((b) (4)) were selected and tested for saccharide content across (b) (4) time points in the PPQ batch. All other serotypes were tested at (b) (4) time points. The justification for the selection of these serotypes are as follows:

(b) (4)

The applicant statistically evaluated a subset of attributes (saccharide content, recoverable volume, and PS-20 content) to demonstrate that the PPQ has a high probability to meet acceptance criteria across the batch. The results from the analysis demonstrated that the upper and lower limits of the high prediction interval for saccharide content, recoverable volume, and PS-20 content fell within the specification limits.

Syringe Filling Dose (b) (4)

The filling dose (b) (4) parameter is classified as a CPP during syringe filling and ensures that the recoverable volume CQA is met. Any syringe containing a filled net (b) (4) outside of the allowable range is rejected. Where a fill (b) (4) is rejected, all syringes filled back until the last acceptable dose (b) (4) check are also rejected. Merck collected data on the filling dose (b) (4) over the fill for each of the (b) (4) needles in operation (see Figure 1 of section 3.2.P.3.5.2). All individual points were observed to be within the control limits, with a low variability from the target fill (b) (4) across the (b) (4) needles in operation.

Deviations

The PPQ had six deviations during its execution. One of the six was due to a deviation from the protocol. Only (b) (4) syringes were intended to be used for PPQ batch 0 (b) (4). However, both (b) (4) and (b) (4) batches were used in this PPQ batch. This deviation does not impact on the PPQ since both syringes are qualified and interchangeable. The remaining five deviations occurred during the manufacturing and laboratory testing. They are as follows:

(b) (4)

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

The process performance qualification demonstrates that the formulation and fill processes for V116 DP are capable of reliably producing consistent product.

3.2.P.4 Control of Excipients

3.2.P.4.1 Specifications

The excipients used in the DP formulation are NaCl, Polysorbate-20, L-Histidine and WFI. The specifications are made to comply with the current version of each referenced (b) (4).

Information Request

While Merck stated that specifications (3.2.P.4.1), analytical procedures, validations of procedures and justification of specifications are based on (b) (4) they did not provide the (b) (4) chapter numbers. Therefore, on December 7, 2023, we sent Merck an Information Request requesting that they provide this information. Merck responded to this request by providing the (b) (4) chapter numbers in amendment 125814/0.6 (sequence number 0007, submitted December 18, 2023; refer to section 1.11, QUALITY INFORMATION AMENDMENT – RESPONSE 2). Their response is acceptable.

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

All analytical procedures for control of excipients are compendial.

3.2.P.4.4 Justification of Specifications

All excipient specifications are compliant with the associated compendial monographs.

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:
The information provided in this section is acceptable.

3.2.P.5 Control of Drug Product

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

Merck established the V116 DP release and stability acceptance criteria in consideration of (b) (4) and commercial-scale manufacturing experience. The release and available stability data from (b) (4) drug product batches (PPQ, Phase 3, and GMP batches manufactured at commercial scale) were analyzed to assess the intended commercial specifications. The release and stability specifications for the DP are presented in Table 1 of section 3.2.P.5.1 SPECIFICATIONS and in the table below.

Table 7. Release and Stability Specifications – Drug Product

Attribute	Acceptance Criteria – Release	Acceptance Criteria – Stability	Test Method
Appearance (Degree of Coloration)	Colorless	Colorless	(b) (4)
Appearance (Opalescence)	Clear to Opalescent	Clear to Opalescent	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)

Identity	Presence of Serotype-Specific Polysaccharides Confirmed	NA	(b) (4)
Saccharide Content (µg/mL)	All Serotypes: (b) (4)	All Serotypes: (b) (4)	
Conjugated Saccharide Content (µg/mL): Serotypes 23B, 24F	(b) (4)	(b) (4) 8	
Conjugated Saccharide Content (µg/mL): Serotypes 15B, 19A, 23A, 35B	(b) (4)	(b) (4)	
Conjugated Saccharide Content (µg/mL): All Other Serotypes	(b) (4)	(b) (4)	
(b) (4)	Calculated	Calculated	
Polysorbate-20 Content (b) (4)	(b) (4)	NA	
(b) (4)	(b) (4)	(b) (4)	
(b) (4)	(b) (4)	(b) (4)	
Recoverable Volume (mL)	0.50 (b) (4)	0.50 (b) (4)	
Syringeability	Liquid is dispensed from the needle in an even stream; no evidence of needle blockage	Liquid is dispensed from the needle in an even stream; no evidence of needle blockage	
Syringe (b) (4)	NA	(b) (4)	
Endotoxin (b) (4)	(b) (4)	NA	
Sterility	No Growth	No Growth	
Container Closure Integrity	NA	(b) (4)	

Justification of Specifications

Appearance – Degree of Coloration

This test method is (b) (4) and complies with (b) (4) .

Appearance-Opalescence

The test method is (b) (4) and complies with (b) (4) .

(b) (4)

Identity

Identity is monitored to ensure that each serotype is added to the formulation. The commercial specification of “Presence of Serotype-Specific Polysaccharides Confirmed” allows for confirmation of identity.

Saccharide Content

This method determines the total saccharide content (conjugated (b) (4)) per serotype and is performed for release and stability. The proposed commercial saccharide content specifications are consistent with the existing specifications for Phase 3/PSS/PPQ. Due to the limited data set of for commercial batches the release specification for saccharide content is (b) (4) of the target and (b) (4) of the target for stability. The proposed specifications are broad. Therefore, we sent an IR to Merck on April 12, 2024, recommending that they revisit the Saccharide Content assay acceptance criteria after accumulation of a minimum of (b) (4) commercial batches to evaluate the process capability and estimate specification limits. Merck responded on April 19, 2024, in amendment 25 (STN 125814/0.25, Sequence Number 0029) committing to reevaluating the Saccharide Content assay specification after a minimum of (b) (4) commercial batches. See “Information Requests,” below, for more information.

Conjugated Saccharide Content

This method is used to measure the conjugated saccharide content in samples in a serotype-specific manner. (b) (4)

(b) (4) The DP acceptance criteria for conjugated saccharide content represent (b) (4) of the average amount of conjugated saccharide at release (b) (4)

(b) (4) All data generated to date have met the proposed specifications. However, DP with conjugated saccharide content at the lower limits of acceptance would fall well below the target DP conjugated saccharide content of 4 µg. Furthermore, the V116 PPQ results for conjugated saccharide content, provided in Figure 4 of section 3.3.2.P.5.6 JUSTIFICATION OF SPECIFICATION, demonstrate that the commercial manufacturing process yields conjugated saccharide content at least (b) (4)-fold higher than the lower limit of the acceptance criteria. Therefore, we sent an IR to Merck on March 22, 2024, requesting they clarify why they set the acceptance criteria so far below the target concentration of 4 µg. They responded on March 29, 2024, in amendment 20 (STN 125814/0.20, Sequence Number 0021) stating that the specifications are wide due to limited number of commercial batches. However, they committed to re-evaluating their specification after a minimum of (b) (4) commercial batches. See “Information Requests,” below, for more information.

(b) (4)

(b) (4)

Polysorbate-20 Content

This method is compendial and complies with (b) (4). The target concentration of PS-20 is (b) (4) with an acceptance criterion of (b) (4) from the target. In their accelerated stability study, Merck demonstrated that there is little to no change in conjugated saccharide content in the DP with PS-20 concentrations of (b) (4). In addition, PS-20 content remains table through (b) (4) of storage at (b) (4) and through (b) (4) of storage at (b) (4). Therefore, Merck concluded that PS-20 is not a stability-indicating attribute and will only monitor this attribute at release.

(b) (4)

(b) (4)

Recoverable Volume and Syringeability

Recoverable volume measurement is required as per (b) (4). The target does to be administered is 0.5 mL. The Recoverable Volume upper limit was established at (b) (4) mL to align with the upper acceptance limit for the fill volume during DP manufacture. The acceptance criteria for release and stability are 0.50 (b) (4) mL. Syringeability is included as a part of the removeable volume method to confirm the functionality of the syringe.

Syringe Functionality – (b) (4)

(b) (4) testing is performed to monitor syringe functionality. The requirement of (b) (4) was established and supported by stability data to date.

Endotoxin

Endotoxin content is performed in alignment with (b) (4), following (b) (4) method (b) (4). The acceptance criterion for release of DP is (b) (4).

Sterility

Sterility is tested in alignment with (b) (4) following (b) (4) method (b) (4). The release and stability acceptance criterion for sterility is “No Growth.”

Container Closure Integrity

CCI is performed on stability to meet (b) (4) requirements per (b) (4). A review of available stability data confirms the ability to routinely meet the established CCI limit of “No leaks detected.”

Chloride Content

Chloride content was evaluated during Phase 3, PSS, and PPQ with acceptance criteria “Characterization Only.” The statistical analysis of representative batches confirms process capability to consistently meet a range within the 95% geometric prediction interval of the chloride concentration of (b) (4).

(b) (4)

Histidine Content

Histidine content was evaluated during Phase 3, PSS, and PPQ with the acceptance criterion “Characterization Only.” The statistical analysis of representative batches confirms process capability to consistently meet a range within 95% geometric prediction interval of the histidine concentration of 20 mM.

(b) (4)

Information Requests

We sent IRs to Merck on **March 22, 2024**, and **April 12, 2024**, concerning the specification ranges of the conjugated saccharide content and saccharide content assays, respectively. Merck provided responses on March 29, 2024 (STN125814/0.20, Sequence Number 0021) and April 19, 2024 (STN125814/0.25, Sequence Number 0029).

March 22, 2024, CBER Comment 6: *In Table 1 of section 3.2.P.5.1 SPECIFICATIONS, you have provided the release specification for conjugated saccharide content of the drug product (DP). The acceptance criteria for conjugate saccharide content are:* (b) (4)

However, DP with conjugate saccharide content at the lower limits of acceptance would fall well below the target DP conjugate saccharide content of 4 µg. Furthermore, the V116 PPQ results for conjugate saccharide content, provided in Table 12 of section 3.2.P.3.5.2 PROCESS VALIDATION AND/OR EVALUATION – DRUG PRODUCT PROCESS VALIDATION, demonstrate that your commercial manufacturing process yields conjugate saccharide content at least twofold higher than the lower limit of the acceptance criteria. Therefore, please clarify why you set your acceptance criteria for conjugate saccharide content so far below the target concentration of 4 µg. Please provide the data, in an analyzable format, that were used to set the acceptance criteria as well as the statistical method/formulas.

Response: Merck agreed to tighten the acceptance criteria for the Conjugated Saccharide Content (b) (4), and provided a commitment shown italics below.

The response is acceptable.

“The Company acknowledges that the available V116 DP batch data for conjugated saccharide is approximately (b) (4) -fold higher than the calculated lower specification limit. However, with limited commercial DS and DP manufacturing experience, a statistically derived specification at this time may not accurately reflect long-term commercial process and analytical variability. Therefore, we commit to re-evaluate the release and stability specification for conjugated saccharide content after an appropriate amount of commercial batch data is generated (i.e., a minimum of (b) (4) commercial batches).”

April 12, 2024, CBER comment 2: *In your submission, you provide acceptance criteria ranges for the Saccharide Content drug product (DP). Your acceptance criteria ranges for the Saccharide Content drug product (DP) release test (section 3.2.P.5.1) appear broad at (b) (4) of target based on the batch release data presented in the submission. Please provide updated stability acceptance ranges for the Saccharide Content assay based upon a statistical analysis of your current data and stability projection estimates. We recommend that you reevaluate your Saccharide Content test acceptance criteria after accumulation of a minimum of (b) (4) commercial batches to evaluate the process capability and estimate specification limits. Please acknowledge.*

Response: Merck has agreed to tighten the acceptance criteria for the Saccharide Content (b) (4) assay after the accumulation of a minimum of (b) (4) commercial batches. In addition, Merck has changed the stability saccharide content specification from (b) (4) of the target to (b) (4) of the target. Sections 3.2.P.5.1 and 3.2.P.5.6 were updated to reflect the new specifications.

The response is acceptable.

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

The specifications and justification for the DP are adequate except for Saccharide and Conjugate Saccharide Content. These specifications are currently well below the target. Merck has justified these specifications due to the low amount of data for these assays. This justification is acceptable given that Merck has committed, in responses to our March 22, 2024, and April 12, 2024, Information Requests, to reevaluate these release and stability specifications.

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

The following analytical procedures and their validations were reviewed by the DBSQC; please refer to DBSQC memos for details on these analytical procedures and their validations: Appearance, (b) (4), Identity, PS-20, (b) (4)

Recoverable Syringe Volume, Endotoxin, (b) (4), and Sterility. Container Closure and Integrity and its associated validation were reviewed by DMPQ.

This section will focus on the following analytical procedures and their validations: Saccharide Content, Conjugated Saccharide Content, and (b) (4).

Saccharide Content

Saccharide content is a DP release parameter that measures the total amount of saccharide (b) (4) that is present in the DP using a (b) (4). This method is also used to confirm identity of each (b) (4) component in the DP. In the method, (b) (4)

The validation of the (b) (4) method was performed in (b) (4) Building (b) (4) in accordance with ICH Q2(R1) and as described in 56085-2021-Report-V4.0-MMD02342672. The validation focused on accuracy, linearity, range, precision (repeatability and intermediate precision), and specificity with predefined acceptance criteria. Robustness studies were conducted as part of final method development prior to formal method validation studies. The method was validated using all 21 serotypes of V116. All predetermined acceptance criteria were met.

Merck used (b) (4) for the validation study. However, they have implemented for routine testing use of (b) (4). Merck states that the implementation of the (b) (4) is supported by (b) (4)

Merck did not provide the referenced equivalency study. Therefore, we sent an Information Request on March 22, 2024, requesting the study report (see "Information Requests," below).

The equivalency study presented in the IR response was conducted with V114 to demonstrate equivalency of (b) (4)

(b) (4)

Though the results demonstrated equivalency, Merck did not indicate why they have decided to routinely use the (b) (4) when they had originally desired to use the (b) (4). In addition, they did not provide documentation on the shelf-life of the (b) (4). Therefore, we sent an additional Information Request to Merck on April 12, 2024. Merck responded on April 19, 2024 (STN 125814/0.25, Sequence Number 0029); please see “Information Requests,” below.

Though the (b) (4) method for Saccharide Content was successfully validated at (b) (4), the manufacturing site responsible for DP release testing for saccharide content is MSD (b) (4). Therefore, Merck performed a method transfer qualification from (b) (4) to (b) (4). They provided in section 3.2.R a technical report titled “*Report for Transfer of Method ATM-22859 “Saccharide Assay and Identity (b) (4)” from (b) (4) to MSD (b) (4) for Testing of V116 (Pneumococcal Conjugate Vaccine) Drug Product,*” which includes details of the transfer study. The transfer study was executed to demonstrate equivalence by showing that (b) (4) can produce analytical results comparable to those generated at (b) (4). To this end, the applicant assessed the relative difference between laboratories and intermediate precision of both laboratories to demonstrate equivalency between the laboratories.

The transfer study was designed using a subset of (b) (4) serotypes ((b) (4)) as representatives of all 21 serotypes. Merck stated in section 3.2.P.5.3.11 VALIDATION OF ANALYTICAL PROCEDURES – IDENTITY AND SACCHARIDE CONTENT that the representative serotypes were selected as they span the full range of (b) (4) that are used in the assay based on (b) (4)

However, this justification was inadequate as it is unclear what the applicant meant by “(b) (4),” and they did not provide a clear demonstration that the representative serotypes are suitable to serve as representatives. Therefore, we sent an Information Request to the firm on March 22, 2024, requesting clarification and adequate justification for their selected representative serotypes (see “Information Requests,” below).

Merck responded to our Information Request on March 29, 2024 (STN125814/0.20, Sequence Number 0021) clarifying that apart from the (b) (4)

In addition, Merck clarified that,

although serotypes (b) (4) cover a variety of polysaccharide (b) (4), they were not selected specifically because they represent specific polysaccharide (b) (4).

Conjugated Saccharide Content

The conjugated saccharide content assay is an (b) (4) method that is used to quantify the conjugated saccharide content in the DP in a serotype-specific manner. The reference standards and DP samples are (b) (4)

The assay method was successfully validated at (b) (4) as described in “*Validation Report for Conjugated Saccharide Content (b) (4) for V116 Pneumoconjugate Vaccine (1-P-QM-WI-9097820 (TM-SV-280))*.” The validation focused on accuracy, linearity, range, precision (repeatability and intermediate precision), and specificity with predefined acceptance criteria. The conjugated saccharide content assay was transferred from (b) (4) to (b) (4). Merck executed a transfer study (*Report for Transfer of Method ATM-23029 “Conjugated Saccharide Content – (b) (4)” from (b) (4) to MSD (b) (4) for Testing of V116 (Pneumococcal Conjugate Vaccine) Drug Product*) to demonstrate equivalency of the (b) (4) and (b) (4) labs by evaluating intermediate precision and relative difference between the labs. A representative subset of serotypes ((b) (4)) were assessed to qualify DP testing for all 21 serotypes of V116. Merck selected these serotypes because their starting concentrations span the full range of (b) (4) used in the assay and their polysaccharide (b) (4). However, as described for the Saccharide Content assay, above, this justification was inadequate as it is unclear what the applicant meant by “(b) (4)” and they did not provide a clear demonstration that the representative serotypes are suitable to serve as representatives. Therefore, we sent an IR to the firm on March 22, 2024, requesting clarification and adequate justification for their selected representative serotypes (see “Information Requests,” below). Merck responded to this request on March 29, 2024 (STN125814/0.20, Sequence Number 0021).

(b) (4)

Information Requests

- We sent the following IRs to Merck on **March 22, 2024**. The applicant conveyed their response on March 29, 2024 (STN125814/0.20, Sequence Number 0021).

CBER Comment 1: *In the validation report 56085-2021-Report-V4.0-MMD02342672, Report for Validation of V116 DP in SOP-15239 “Total Polysaccharide (Ps) (b) (4) for Pneumococcal Conjugate Vaccine (V116)” at (b) (4), you state that the SOP-15239 “Total Polysaccharide (Ps) (b) (4) for Pneumococcal Conjugate Vaccine (V116),” formerly known as ASOP 29-VBA-627, was updated to version 2.0 with the updates discussed in 56085-2020- Protocol-V2.0-MMD01832357, Protocol for Validation of V116 DP in ASOP 29-VBA-627 Total Polysaccharide (Ps) (b) (4) for Pneumococcal Conjugate Vaccine at (b) (4). However, you have not included the SOP or the validation protocol. For us to be able to adequately assess the suitability of your (b) (4) method for determining saccharide content, please provide SOP-15239 “Total Polysaccharide (Ps) (b) (4) for Pneumococcal Conjugate Vaccine (V116)” and “56085-2020-Protocol-V2.0-MMD01832357, Protocol for Validation of V116 DP in ASOP 29- VBA-627” for review.*

Response: Merck has provided the requested documents for review.

The SOP and validation protocol provided were complete and provided clear instructions on the execution of the (b) (4) method for total saccharide content as well as the steps followed for the validation study. The response is acceptable.

CBER Comment 2: *On page 2 of section 3.2.P.5.3.11 VALIDATION OF ANALYTICAL PROCEDURES – IDENTITY AND SACCHARIDE CONTENT, where you describe the method transfer of the identity and saccharide content, from (b) (4) to (b) (4) you state that you assessed drug product (DP) samples for the representative serotypes (b) (4) to qualify DP testing for all 21 serotypes in V116. In addition, you state that you selected these serotypes because they span the (b) (4) that are used in the assay based on starting concentration, and their polysaccharide (b) (4). However, this justification is inadequate as you have not clearly indicated what you mean by “as they span the (b) (4) that are used in the assay based on starting concentration.” Furthermore, you have not provided adequate justification for why the selected serotypes are suitable for representing all 21 serotypes. Therefore, to support that the selected serotypes are truly representative of all the serotypes produced in V116 and thus, your validation study data are supportive of the assay’s intended use, please provide a detailed justification outlining why each of selected serotypes are suitable representatives.*

Response: Merck states that depending on the serotype being tested, reference standards and samples are (b) (4)

. In addition, Merck clarifies though serotypes (b) (4)

cover a variety of polysaccharide (b) (4) they were not selected for this characteristic.

We followed up with additional IRs from myself and the CMC statistician, sent on **April 18, 2024**. Merck responded under STN 125814/0.26, Sequence Number 0030, on April 25, 2024. These are discussed further below.

CBER Comment 3: On page 2 In section 3.2.P.5.3.12 VALIDATION OF ANALYTICAL PROCEDURES – CONJUGATED SACCHARIDE CONTENT is a description of the method transfer of the identity and saccharide content from (b) (4) to (b) (4), you state that drug product (DP) samples were assessed for the representative serotypes (b) (4) to qualify DP testing for all 21 serotypes in V116. As described in comment 2, above, you have not provided adequate justification as to how these serotypes are representative of all 21 serotypes and without this information, we cannot properly evaluate your assay validation and the suitability of the assay for its intended use. Please provide a detailed justification outlining why each of selected serotypes are suitable representatives.

Response: Merck states that, depending on the serotype being tested, (b) (4) (serotypes (b) (4)). In addition, Merck clarifies though serotypes (b) (4) over a variety of polysaccharide (b) (4), they were not selected for this characteristic.

CBER Comment 5: In your description of your (b) (4) method to determine saccharide content on page 2 of section 3.2.P.5.3.11 VALIDATION OF ANALYTICAL PROCEDURES - IDENTITY AND SACCHARIDE CONTENT, you state that you validated the (b) (4) method using (b) (4). In addition, you state that in routine testing you use the (b) (4) used in the validation, and that the implementation of the (b) (4) is supported by an equivalency study (b) (4) for serotypes (b) (4) and the (b) (4). However, you have not provided this study and thus you have not demonstrated equivalence of the (b) (4). Therefore, please provide the equivalency study. Without this information we cannot determine that your assay is valid for its intended, routine use.

Response: Merck provided the following equivalency study and reagent qualification studies:

- *BVA-2021-MISC-v6.0-PRO-010056785, Miscellaneous Document for the Qualification and Certificate of Analysis of (b) (4) for Use in (b) (4), V114 and V116*

- 56085-2021-Report-v2.0-MMD02519224, Report for Qualification of (b) (4) (b) (4) Lots for Use in Pneumoconjugate Vaccine (V116) Methods SOP-15239 and ATM-22859
- V114 (b) (4) Critical Reagent Qualification and Performance Evaluation

The equivalency of the (b) (4) was studied for the V114 program. The equivalency study assessed suitability of the use of the (b) (4). Merck demonstrated equivalency of (b) (4) by assessing the performance of the (b) (4). The study assessed relative accuracy, dilutional linearity, specificity, and intermediate precision. In addition, the applicant conducted a reagent qualification study for the (b) (4) by (b) (4). The results of the equivalency and reagent qualification studies demonstrated that the (b) (4) are comparable to the (b) (4). Though the results demonstrated equivalency, they did not make clear why they decided to routinely use the (b) (4) when they had originally desired to use the (b) (4). In addition, Merck did not provide documentation on the shelf-life of the (b) (4). Therefore, we sent an additional IR on April 12, 2024 (see “Information Requests” below). Merck responded to that request on April 19, 2024 (STN125814/0.25, Sequence Number 0029).

- We sent the following Information Request to Merck on **April 12, 2024**. The applicant conveyed their response on April 19, 2024 (STN125814/0.25, Sequence Number 0029).

CBER Comment 4: In your response in amendment 20 (STN125814/0.20), you provide the technical report which summarizes the equivalency study used to demonstrate the equivalency of the (b) (4) in the total saccharide (b) (4) assay. The purpose of this study was to evaluate the performance of the (b) (4) reagents compared to (b) (4) reagents to demonstrate comparability. On page 4 of the study, you state that “Industry standard practice generally involves storing (b) (4) reagents as (b) (4)

Please clarify why you have decided to routinely use liquid antibody reagents instead of (b) (4) reagents. In addition, please provide documentation that the (b) (4) reagents are being used within their established shelf-life and data that demonstrate that throughout this shelf life the (b) (4) perform at a level that is comparable to their initial introduction.

Response: Merck clarified the decision to use (b) (4) was due to operating efficiency. The (b) (4) required added processing time,

resources, and storage space that Merck had not initially anticipated which led to their discontinued use. In addition, Merck has provided the shelf life ((b) (4)) and shelf-life justification for the (b) (4) and a protocol for the evaluation of shelf-life extension for the (b) (4) to support its use in the (b) (4) assays. Their response is acceptable.

- We sent the following Information Requests to Merck on **April 18, 2024**. The applicant conveyed their response on April 25, 2024 (STN125814/0.26, Sequence Number 0030). Comments 1–5 were from the statistical reviewer and will be covered in their memo. Comments 6 and 7 are reviewed herein.

CBER Comment 6: *Your transfer strategy for the DP Saccharide Assay from (b) (4) to (b) (4) for V116 relies on a validation study previously generated for your V114 product. This is based on your assertion that the V114 identity and saccharide content method is highly similar to the V116 identity and saccharide content method. That study demonstrated method reproducibility for representative serotypes (b) (4) to qualify the method from (b) (4) to (b) (4) for all 15 serotypes in V114. The V114 DP contains an adjuvant, therefore must undergo a (b) (4) step as part of the method. V116 does not contain an adjuvant and is not subjected to the additional steps. If (b) (4) is not 100%, this has the potential to affect validation results. You have not provided evidence that the V116 and V114 DP test methods yield equivalent results, therefore it is not adequate to rely on the data generated at (b) (4) for V116 using the V114 DP test method to infer the method has been adequately transferred to (b) (4) for V116. Additionally, of the (b) (4) representative serotypes studied, only serotype (b) (4) is contained in V116. Please provide data that demonstrates the performance characteristics of the V114 assay (with (b) (4)) is equivalent to the V116 assay (without (b) (4)). Provide a rationale why the (b) (4) serotypes tested ((b) (4)) would adequately represent the 21 serotypes in V116?*

Response: Merck acknowledged the differences between V114 and V116 but deemed the presence of the adjuvant, and the associated requirement to (b) (4) for V114 prior to analysis, as only a minor difference. To alleviate any differences the company performed a supplemental study to assess the equivalency between (b) (4), as described in “Report for Supplemental Study for the Equivalency Assessment of Method ATM-22859, “Saccharide Assay and Identity ((b) (4))” at Merck (b) (4) and MSD (b) (4)”, QLMAS-2024-Reportv1.0-PRO-013729244. Formulated samples were tested that spanned the range of the assay ((b) (4)) and compared to commercial material. The assessment utilized a subset of (b) (4) serotypes ((b) (4)) and the acceptance criterion for equivalence ((b) (4)) was established based on characteristics assessed as part of the original method validation and in consideration of product release specifications. The supplemental study concluded that results met the pre-defined criteria, which further supports equivalency between the laboratories across the range of the assay. Therefore, the (b) (4) lab is qualified to perform the V116 saccharide content (b) (4). Additionally, Merck provided a

summary from a small study to demonstrate no difference in results between formulations from V114 (with adjuvant) and V116 (without adjuvant). Results showed a negligible (b) (4) difference; however, no details or data were provided.

CBER Comment 7: *In the DP Saccharide validation report you report two deviations involving serotype (b) (4) that necessitated re-testing. In deviation #2 (b) (4)*

(b) (4) You reasoned that the variability failure was due to (b) (4). It is not clear from your procedure how the (b) (4) caused the failures considering the (b) (4) would not be expected to be affected by the (b) (4). Please provide a thorough explanation of the failures, including the raw data for our review. Please update your test method procedure to include the (b) (4). In deviation #8, during repeatability testing of a sample, serotype (b) (4) failed due to not meeting the sample points acceptance criteria. As per your validation plan, you were allowed to re-test. Please provide the raw data outputs ((b) (4)) and calculated results from the original and re-test results.

Response: In deviation #2 Merck states that (b) (4)

(b) (4) For related deviation #8, I requested the raw data, but Merck only provided references to the notebooks where the data can be found. Merck did not provide data because results are not generated when assay acceptance criteria are not met, and so they indicated that, therefore, a comparison of the original and re-test results could not be provided. The root cause for many of the deviations was related to the (b) (4); therefore the revisions to the procedure are expected to alleviate future related occurrences.

Overall Reviewer’s Assessment of Sections 3.2.P.5.2 and 3.2.P.5.3:

I reviewed the analytical procedures and validations for the assays described above. In addition to validation studies, Merck also executed method transfer studies since the validation of the Saccharide Content and Conjugated Saccharide Content assays were performed at a location different from the routine testing sites ((b) (4)). The validation studies were found to be acceptable. Please see the CMC statistician’s memo for a review of method transfer of the saccharide content assay and the associated IRs conveyed to Merck on April 18, 2024, with responses received on April 25, 2024 (STN125814/0.26, Sequence Number 0030).

3.2.P.5.4 Batch Analyses

Information on batches manufactured for use in clinical studies, primary stability studies, and PPQ are presented in Table 1 of section 3.2.P.5.4 BATCH ANALYSES. Pre-clinical (toxicology study) and Phase 1/2 clinical batches were manufactured at (b) (4). Phase 3/PSS and PPQ batches were manufactured at (b) (4). The batches were tested to specifications applicable at the time of release and all results were generated with methods in place at the time of testing (see Tables 2–5 of section 3.2.P.5.4 BATCH ANALYSES). The batch release information presented is acceptable.

3.2.P.5.5 Characterization of Impurities

No additional impurities are introduced during the DP manufacturing process. Any potential impurities would most likely be because of (b) (4) and these are monitored by (b) (4) assays.

Merck completed a (b) (4) assessment in accordance with (b) (4). The assessment concluded that there was no risk identified for the presence of (b) (4) in V116 DP from the biological drug substance, excipients, and primary packaging.

A small number of (b) (4) may be present in the parental product. The (b) (4) levels are measured during release and stability and the acceptance criteria are acceptable.

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

The release data for the batches presented in the batch analyses were within specification with no concerning trends observed. The information presented sections 3.2.P.5.4 and 3.2.P.5.5 is acceptable. No deficiencies were identified.

3.2.P.6 Reference Standards or Materials

The reference standard used in the determination of total saccharide content and conjugated saccharide content is generated using primary reference standard (PRS) and secondary reference standard (SRS). The PRS is sourced from individual Phase 3 commercial-scale (b) (4) batches (b) (4) for each of the 21 (b) (4) serotypes). The SRS is a blend of the (b) (4) batches used as PRS. The SRS is formulated using the same buffer components as DP except the target (b) (4) is (b) (4) while the target (b) (4) for DP is (b) (4). The (b) (4) target (b) (4) of the SRS was implemented to (b) (4). This strategy for the PRS and SRS provides a quantitative link to clinical studies since (b) (4) individual commercial-scale (b) (4) batches were selected for use as reference standards.

The total saccharide content for the PRS is equivalent to the target (b) (4). The conjugated saccharide concentration of the PRS is calculated based on the (b) (4) method. Merck states that the quantities

of the (b) (4) batches retained for use as PRS are sufficient for preparation of SRS indefinitely.

The SRS are prepared by (b) (4)

The (b) (4) source for PRS is currently on long-term stability study and is expected to meet the (b) (4) shelf-life expectancy. After the initial (b) (4) stability study, the PRS will be monitored on an ongoing basis to identify trends with performance. In addition, a stability study extending to a minimum of (b) (4) will be initiated. The following attributes will be monitored: (b) (4). The stability of the SRS will be monitored (b) (4) against the PRS using the (b) (4) assay. SRS are assigned an initial expiry date of (b) (4) from date of manufacture. After the initial expiry date of (b) (4), the SRS expiry date can be extended beyond the (b) (4) on (b) (4) basis with a maximum expiry date of (b) (4). The PRS and SRS are (b) (4) and stored (b) (4). The storage condition has been selected to align with the long-term storage condition for (b) (4).

Should a need arise to replace the PRS, new (b) (4) batch(es) that meet all the release criteria will be considered acceptable replacements. In the event of catastrophic loss or unacceptable trending/ results, the replacement (b) (4) batch will be calibrated by (b) (4) against the current SRS. The assigned potency of the new PRS is average of potencies against the existing the SRS. For scenarios where replacement is due to low PRS inventory, the (b) (4) batch will be calibrated by (b) (4) against the current PRS. The assigned potency of the new PRS will be relative to that of the current PRS.

SRS batch (b) (4) is currently in use as the first working reference standard. It was formulated on an (b) (4) scale and (b) (4).

Information Requests

In response to an Information Request sent on **December 7, 2023**, (STN 125814/0.6, Sequence Number 0007, submitted December 18, 2023, refer to section 1.11 QUALITY INFORMATION AMENDMENT – RESPONSE 3) Merck committed to provide the following comparability protocols for generating new PRS and SRS. Merck subsequently submitted the comparability protocol (CP) in STN 125814/0.9 (Sequence Number 0010, submitted January 29, 2024). They indicated they will report these changes in their Annual Report.

We did not agree with their proposal to report the changes in the annual report, and sent additional Information Requests. Please see section 3.2.R below for additional details regarding the CP, the Information Requests, and Merck's response.

As part of amendment 9, Merck also updated the acceptance criteria presented in Section 3.2.P.6 REFERENCE STANDARDS AND MATERIALS, Table 2. They revised the acceptance criteria to reflect the current procedure for SRS calibration (requiring a non-PRS source) where the exception for the PRS (b) (4) was removed.

(b) (4)
(b) (4)
This response is acceptable.

3.2.P.7 Container Closure System

The extractables and leachables studies for the syringe were covered in section 3.2.P.2.4 CONTAINER CLOSURE SYSTEM of this memo, and the shipping qualification study is covered in section 3.2.P.3.5 PROCESS VALIDATION AND/OR EVALUATION. The (b) (4) syringes are supplied by (b) (4) and (b) (4), respectively. Syringes are sterilized by (b) (4) and received at the DP manufacturing site ready to use. The glass components of the syringes conform to (b) (4). The plunger stopper is supplied by (b) (4) and conforms to (b) (4). The plunger rod is not part of the container closure system since there is no product contact. The addresses of the sterilization sites are provided in Table 3 of section 3.2.P.7 CONTAINER CLOSURE SYSTEM.

<p>Overall Reviewer's Assessment of Section 3.2.P.7: The information provided in this section is acceptable. I found no deficiencies in section 3.2.P.7.</p>

3.2.P.8 Stability

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

(b) (4) DP batches, which include (b) (4) PSS and (b) (4) PPQ ((b) (4) (b) (4) batches), are enrolled on stability in the PFS container closure system. In addition, (b) (4) pilot-scale batches were provided in support of the proposed shelf life. All batches enrolled on stability were manufactured at the final formulation and fill site (b) (4) using either (b) (4) or (b) (4) syringes, except for the (b) (4) pilot scale batches which were manufactured at (b) (4) (see Table 1 of section 3.2.P.8.1 STABILITY SUMMARY AND CONCLUSION). All batches were held at the recommended storage temperature ($5 \pm 3^{\circ}\text{C}$, (b) (4)). Up to 12 months of stability data are available for the PSS batches and up to 6 months of stability data for the PPQ batches. (b) (4) months of data are available for the (b) (4) pilot-scale batches ((b) (4) (b) (4)). The proposed shelf-life is 18 months.

Merck also performed supportive testing at alternative conditions including at (b) (4) for 30 days to represent (b) (4) excursions, (b) (4) for 14 weeks to represent (b) (4) excursions, and under conditions of (b) (4)

Merck is using the following analytical methods in the stability program: Appearance (Degree of Coloration and Opalescence), (b) (4), Saccharide Content, Conjugated Saccharide Content, (b) (4), Recoverable Volume, Syringeability, Syringe Functionality – (b) (4), and Container Closure Integrity (CCI).

All datapoints for all tests met acceptance criteria for the (b) (4) conditions. All data points met acceptance criteria for the 5°C storage, except for an OOS result for CCI by (b) (4) for batch (b) (4) at the initial time point. After an investigation Merck determined the most probable root cause to be presence of a (b) (4)

Based on an evaluation of the overall risk, the applicant concluded that the OOS result does not represent an increased risk to container closure integrity for the batch and had no impact on product quality.

For the (b) (4) light conditions, the Saccharide Content – (b) (4) acceptance criteria for the study required that the (b) (4) confidence interval (CI) of the (b) (4) When evaluating the results of the photostability studies, serotype (b) (4) showed a statistically significant change in Saccharide Content when exposed to light for the (b) (4) when compared to the control. Additionally, the (b) (4) configuration from (b) (4) and (b) (4) syringe did not conform to specifications for Appearance - Degree of Coloration. The study supports the recommended storage condition for the (b) (4) V116 DP syringes to be “protected from light.”

During BLA review, Merck provided additional stability study data (see STN125814/0.4, Sequence Number 0005) which add support to the proposed shelf life of 18 months. Therefore, the information presented support the proposed 18-month shelf life at 5 ± 3°C.

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

Merck will continue stability studies on the DP PSS batches according to the schedule detailed in the data tables for these batches presented in Section 3.2.P.8.3.1 STABILITY DATA. Additionally, Merck plans to manufacture DP annually and will enroll a minimum of (b) (4) in the commercial stability program at the long-term storage

condition of $5 \pm 3^{\circ}\text{C}$. The applicant will monitor Appearance (Degree of Coloration and, Opalescence) (b) (4), Saccharide Content, Conjugated Saccharide Content, (b) (4), Recoverable Volume, Syringeability, Syringe Functionality – (b) (4), Sterility, and Container Closure Integrity over (b) (4) months. Testing intervals are 0, 6, 12, 18, (b) (4) months except for container closure integrity at 12, (b) (4) months and sterility at 0 and end of shelf life. The stability specifications are provided in Table 1 of section 3.2.P.5.1 SPECIFICATIONS.

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

I found no deficiencies for section 3.2.P.8. The information provided supports an 18-month shelf life for V116 DP when stored at $5 \pm 3^{\circ}\text{C}$.

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

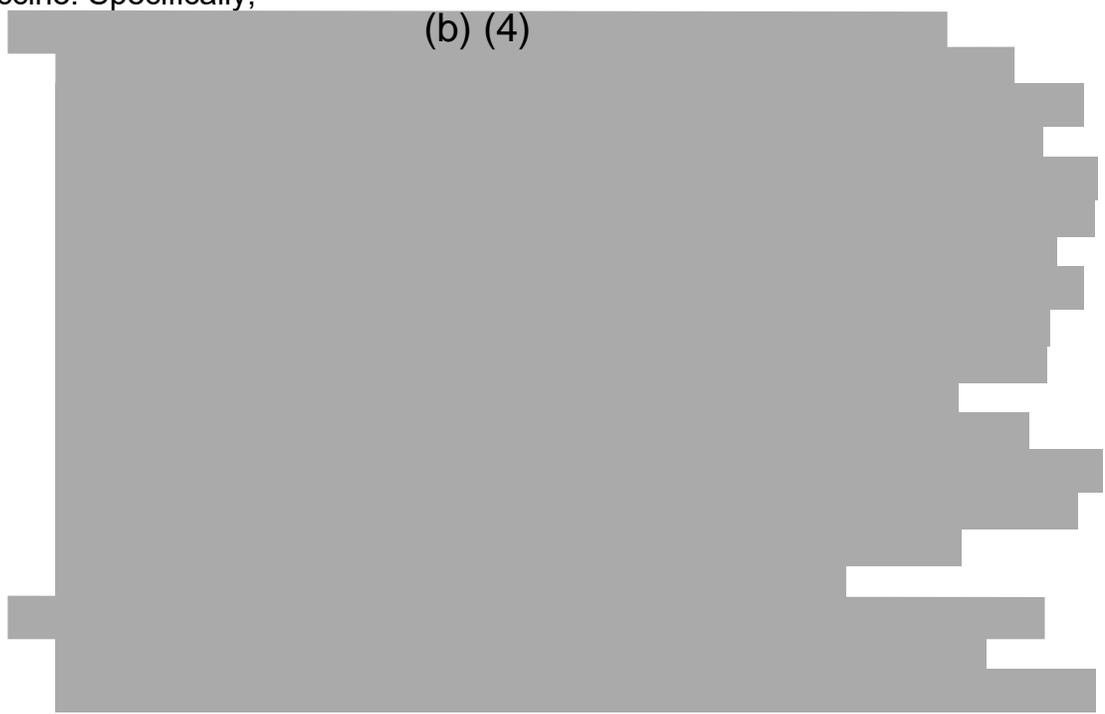
We defer to DMPQ for review of this module.

3.2.A.2 Adventitious Agents Safety Evaluation

The applicant evaluated the following for their V116 adventitious agents safety assessment:

1. **Generation and testing of cell banks:** The applicant states that no live viruses or cell lines of human or animal origin were used in the manufacture of the vaccine. Specifically,

(b) (4)



(b) (4)

2. **Selection and assessment of raw materials with exposure to materials of human or animal origin:** Merck determined that the following raw materials were human or animal-derived raw materials, or raw materials with exposure to materials of human or animal origin, used during the production of the master and working cell banks, drug substance intermediates, drug substance, or drug product.

(b) (4)

(b) (4)

3. **Manufacturing controls:** Merck has implemented a multistep process to prevent the presence of extraneous agents in the vaccine. This includes:
- a. An evaluation of animal-derived raw materials
 - b. A review of raw material vendors
 - c. Testing of all manufacturing process inputs
 - d. Maintenance of classified manufacturing environments
 - e. Testing of personnel involved with manufacturing.

In addition, all vaccine bulks and bulk intermediates are evaluated in a series of tests that demonstrate that the vaccine is free of extraneous agents (see section 3.2.S.2.3 of this memo, above).

4. **Testing of process intermediates:** The manufacturing processes for the DS and DSI contain routine controls to minimize contamination with non-viral agents such as bacteria and fungi. These controls include:
 - a. Environmental controls
 - b. Filtration of process streams and buffers
 - c. Endotoxin and bioburden testing of vaccine bulk and bulk intermediates

Viral Clearance Studies

Not applicable

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

I have reviewed the adventitious safety evaluation. Merck's proposed control strategy is acceptable. No deficiencies were found.

3.2.A.3 Novel Excipients

Not applicable. There are no novel excipients.

3.2.R Regional Information (USA)

Executed Batch Records

Merck did not initially provide executed batch records for the DS or the DP. Therefore, we sent IRs on **January 30, 2024**, and **March 28, 2024**, to request the executed records. Their responses can be found in STN 125814/0.10 (Sequence Number 0011) and STN125814/0.22 (Sequence Number 0023) for DP and DS, respectively (see "Information Request," below).

Master and executed batch records for V116 DP were reviewed for the manufacturing process from (b) (4) through to drug product formulation and fill for serotypes (b) (4).

Merck submitted executed batch records for seven representative serotypes ((b) (4) (b) (4)). The complete executed batch records, including (b) (4) through manufacture of (b) (4) DP, were reviewed for serotypes (b) (4). The executed batch records for the (b) (4) processes were also reviewed for serotypes (b) (4). These executed records chosen for review are representative of the variation in the workflow of the manufacturing process, especially with respect to the DS manufacturing steps.

The reviewed batch records for DS and DP appear complete and no major discrepancies between the executed and master batch records were identified.

Information Requests

We sent the following Information Requests to Merck on **January 30, 2024**, and **March 28, 2024**, to request the executed records. Their responses can be found in

STN 125814/0.10 (Sequence Number 0011) and STN125814/0.22 (Sequence Number 0023) for DP and DS, respectively.

January 30, 2024, CBER Comment 2: In your submission, you provided your master batch records in section 3.2.R. However, you have not provided executed batch records. Per 21 CFR 211.192 and 21 CFR 211.188, firms must submit drug product production and control records relating to the production and control of each batch to support compliance with all established, written procedures. Please submit the executed batch records from at least one validation lot or indicate where in the submission they can be found.

Response: Merck has provided the requested executed batch records for review. The response is acceptable.

March 28, 2024, CBER Comment 1: You provide master batch records for Drug Substance (DS), Drug Product (DP), and the combination assembly in section 3.2.R of your submission. On January 30, 2024, we requested you provide executed batch records, and you responded on February 8, 2024 (SN0011, amendment 10) to provide executed batch records for your DP. However, you have not provided the associated executed batch records for your DS and combination assembly. Completed (i.e., executed) batch records representative of all aspects of the production process are necessary to support that your batches were properly made and recorded. Therefore, please provide executed batch records for the DS and the combination assembly or indicate where in the submission they can be found. Please refer to FDA Guidance for Industry Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product for more information.

Response: Merck has submitted executed batch records for (b) (4) representative serotypes. The representative serotypes were selected based on the following considerations:

(b) (4)

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The response is acceptable.

Method Validation Package

The table below includes a list of the method validation materials we reviewed in this memo, as well as the section of the memo where one can find a review of the validation. Individual file names for each method and report can be found in Tables 1 and 2 of section 3.2.R.8 METHOD, VALIDATION, VERIFICATION, ROBUSTNESS, AND

TRANSFER REPORT SUMMARY (MBC AND DP). Please refer to DBSQC memos for the methods not listed here.

Test	Method	Reviewed in Section
DP-Saccharide Content	(b) (4)	3.2.P.5.2 and 3.2.P.5.3
DP-Conjugate Saccharide Content		3.2.P.5.2 and 3.2.P.5.3
DP- (b) (4)		3.2.P.5.2 and 3.2.P.5.3
(b) (4)		3.2.S.4.2 and 3.2.S.4.3
(b) (4)		3.2.S.4.2 and 3.2.S.4.3
(b) (4)		3.2.S.4.2 and 3.2.S.4.3
(b) (4)		3.2.S.4.2 and 3.2.S.4.3
(b) (4)		3.2.S.4.2 and 3.2.S.4.3

Combination Products

We defer this section to the Device Reviewer.

Comparability Protocols

(b) (4)

[Redacted content]

Reference Standards for DP

This CP describes the plan for the introduction of new DP primary and secondary reference standards (PRS and SRS, respectively). The CP also includes the plan for the shelf-life extension of the SRS. Merck has proposed to notify CBER of the extension of shelf life of the SRS and the introduction of new PRS and SRS via Annual Report. The annual report will include summaries of the serotype-specific (b) (4) release data and calibration test results. Based on subsequent communications, Merck will submit introduction of new PRS under the CBE-30 reporting category, and introduction of new SRS in the annual report (see “Information Requests,” below, for discussion of reporting category and the final decision). Changes to the described CP will require a new protocol which Merck will submit to CBER as a PAS.

The current PRS batches were used to formulate the Phase 3 clinical DP batches and thus maintain a link to the clinical data. (b) (4) batches of each of the 21 pneumococcal conjugate (b) (4) DS were designated for indefinite use for each of the (b) (4) PRS. Merck has provided a procedure for the introduction of future PRS in the event of catastrophic loss or low inventory.

SRS are formulated at an (b) (4) scale by (b) (4). Additional calibration is not required for the current SRS since it prepared using the PRS. However, if a non-PRS is required to prepare future SRS, calibration testing will be required. The calibration method implemented will depend on one of the following reasons for the replacement of the PRS:

- Stability issue/irreplaceable loss (i.e., storage unit malfunction)
- Low inventory

In the event of stability issue/irreplaceable loss, the replacement primary (b) (4) batch(es) will be calibrated by (b) (4) against the current, valid SRS which has been qualified and is within its re-evaluation date. The assigned potency of the new PRS is the geometric mean of the PRS potencies against the existing SRS. In the case of low inventory, the replacement primary MBC batch(es) will be calibrated by (b) (4) against the current PRS. The assigned potency of the new PRS is the geometric mean of the new PRS potencies the PRS calibrated based on the existing PRS.

Information Requests

We sent the following Information Request to Merck on **March 28, 2024**. The applicant conveyed their response on April 5, 2024 (STN125814/0.22, Sequence Number 0023).

CBER Comment 2: In amendment 9 (STN125814/0.9), you submitted post-approval change management protocols (PACMP) for the introduction of new reference standards for (b) (4) DP. We have the following requests regarding the PACMP:

- a. You propose to report the introduction of new reference standards via Annual Report. We do not agree with your proposal. Because new reference standards have a moderate potential to affect product quality, please report a change of reference standards as a CBE-30. Please acknowledge.*
- b. In the PACMP for (b) (4) you have cross referenced Section 3.2.S.5.1 Reference Standards or Materials (b) (4) for your description of the procedures for qualification and recertification of the reference standards, in place of providing a detailed description of your protocol. Per FDA Guidance for Industry Comparability Protocols for Post approval Changes to the Chemistry, Manufacturing, and Controls Information in an NDA, ANDA, or BLA, “a comparability protocol should provide a comprehensive, detailed plan for the implementation of a proposed change.” In addition to cross-referenced section, please provide a complete description of the protocol you plan to implement for the qualification and recertification of reference standards.*

Response: Merck responded in on April 5, 2024, in amendment 22 (STN125814/0.22, Sequence Number 0023) with an updated comparability protocol detailing the procedures for qualification and recertification of the reference standards for the (b) (4). Merck cited FDA guidance in support of their proposal to introduce new reference standards for (b) (4) DP in their Annual Report. They state that risk to product quality is low since the protocol would have been reviewed and approved by FDA. In addition, they state that the DP reference standards qualification strategy and protocol mitigates the risk to product quality due to their use of clinically linked reference standards.

We did not agree with this justification. Therefore, we sent another IR on **April 12, 2024**, notifying them that we do not agree and requested that they submit the introduction of new reference standards in a CBE-30. Merck responded to our IR on April 19, 2024 (STN125814/0.25, Sequence Number 0029).

CBER Comment 3: *In your response in amendment 22 (STN 125814/22, received on April 5, 2024) to our IR comment 2 (transmitted on March 28, 2024) you cite FDA guidance to support your proposal to introduce new reference standards for (b) (4) DP via Annual Report. You state that risk to product quality is low since the protocol would have been reviewed and approved by FDA. In addition, you state that the DP reference standards qualification strategy and protocol mitigates the risk to product quality due to their clinical link. While this may be true, the SRS is formulated differently from the (b) (4) DP, and you have not provided sufficient long-term stability data for the SRS reference lots as formulated. Furthermore, you state in your Post-Approval Change Management Protocol (PACMP), "Should a need arise for the use of one or more (b) (4) from a non-PRS, additional qualification will be performed to avoid potential shifts in the reference standard." Thus, if there is a loss of the PRS samples you would be introducing reference standards that are not linked to the Phase 3 clinical trial lots. Therefore, we do not agree with your proposal to report the introduction of new reference standards in an Annual Report. Please report the introduction of new reference standards as a CBE-30.*

Response: To support reporting the introduction of new SRS in an annual Merck has submitted Phase 1 and Phase 2 stability results for the SRS. The stability data presented demonstrate that the SRS is stable over the (b) (4) shelf life. In addition, Merck has acknowledged our concerns about the use of future PRS not being linked to the Phase 3 clinical trial lots and has agreed to report the introduction of new PRS as a CBE-30.

Merck has presented adequate stability data to demonstrate that there is minimal risk to use qualified SRS. Therefore, we agree that it suitable to submit the introduction of new SRS in their annual report. Their response is acceptable.

Other eCTD Modules

Module 1

A. Environmental Assessment or Claim of Categorical Exclusion

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

B. Reference Product Designation Request

The applicant filed a claim of exclusivity on October 18, 2023, claiming there are no licensed biological products that are structurally related to the Capvaxive vaccine for which they or one of their affiliates, licensors, predecessors in interest, or related entities is the current or previous license holder. Merck has two other licensed Pneumococcal vaccine products. They believe that Capvaxive is not structurally related to Pneumovax 23 because Capvaxive will affect different molecular targets, i.e., Capvaxive contains PS from different *S. pneumoniae* serotypes. Additionally, Capvaxive includes a carrier protein (CRM197) while Pneumovax 23 does not. For these reasons, the applicant expects that the two vaccines would differ in potency. The other licensed Pneumococcal vaccine from the Merck, Vaxneuvance, also differs from Capvaxive with regards to molecular targets as Capvaxive includes PS from different serotypes and thus, Merck contends that the two products will differ in potency for the serotypes present in one vaccine but not the other.

Capvaxive includes nine serotypes that are not included in Pneumovax 23 and 15 serotypes that are not included in Vaxneuvance. The differences in serotype composition make Capvaxive unique relative to these two other vaccines and will alter the potency of Capvaxive.

Both Capvaxive and Vaxneuvance include PS individually conjugated to the carrier protein CRM197. Pneumovax 23 does not include a carrier protein, which is a key difference between this vaccine and Capvaxive. Additionally, while Vaxneuvance and Capvaxive both include PS conjugated to CRM197, the solvents used to conjugate antigens in each vaccine differ. The different solvents lead to different conjugation reaction efficiencies which, in turn, could affect immunogenicity of the vaccine. Vaxneuvance also includes aluminum adjuvant while Capvaxive does not include adjuvant, which will change the potency of the vaccine. Therefore, the combination of pneumococcal polysaccharides included in Capvaxive is unique relative to other U.S.-licensed products.

The CMC review team recommends granting exclusivity. Upon finalization of this memo, the Reference Product Exclusivity Board had not yet met to discuss. If approved, the product will be designated as a reference product and the associated exclusivity periods will be based upon the first date of approval.

C. Labeling Review

Full Prescribing Information (PI):

Prescribing information in the Package Insert (PI) contains information about the dosage, form, and strength of CAPVAXIVE, a description of its contents, a summary of the clinical pharmacology supporting its indication and instructions on storage and handling. In brief, the PI states that CAPVAXIVE is a colorless, clear to opalescent sterile solution of purified capsular polysaccharides from *S. pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B (de-O-acetylated prior to conjugation), 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B individually conjugated to CRM197 carrier protein.

Vaccination with CAPVAXIVE induces OPA against 22 *S. pneumoniae* serotypes. Serotype 15C represents the immune response to the deOAc15B polysaccharide as the molecular structure for deOAc15B and 15C are similar.

CAPVAXIVE is supplied in cartons of one or 10 0.5-mL single-dose prefilled Luer Lock syringes with tip caps. The vaccine should be stored at 2–8°C protected from light and should not be frozen.

Carton and Container Label:

The primary and secondary container cartons were reviewed, and the information provided corresponds with DP contents described in Section 3.2.P.1.1 DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT. This is acceptable.

Modules 4 and 5

Reviewed by JS

Module 4

Nonclinical Studies

4.2 Study Reports

PD001^{(b) (4)}-0231 V116: Immunogenicity And Protection In Mice Amendment 1

Merck used (b) (4) mice (Study V116 MS-5B) and (b) (4) mice (Study V116 MS-10) to evaluate the immunogenicity of V116. They initially used V116 containing polysaccharide from serotype (b) (4) instead of (b) (4) (study MS-5B), and subsequently (study MS-10) switched to V116 with serotype (b) (4) polysaccharides replacing (b) (4) to demonstrate cross-reactivity between (b) (4). They administered V116 into (b) (4) mice intraperitoneally and (b) (4) mice intramuscularly on Days 0, 14, and 28, and collected blood samples on Day 35 to analyze serotype-specific IgG titers in an electrochemiluminescent assay (ECL) and functional antibody titers in a multiplexed opsonophagocytosis assay (MOPA). In both studies MS-5B and MS-10, V116 elicited comparable IgG titers and OPA titers against 15B and 15C, suggesting cross-reactivity between 15C and 15B. In study MS-10, they assessed IgG titers and OPA titers against (b) (4) and demonstrated that V116 elicited immunogenicity against (b) (4) via cross-reactivity

with (b) (4). They also challenged mice intratracheally with a lethal dose (10^5 CFU) of *S. pneumoniae* serotype 24F at Day 49. V116 elicited IgG antibodies against all 21 serotypes. V116 also induced functional antibodies against all 21 serotypes and protected mice from challenge with *S. pneumoniae* serotype 24F.

PD002 (b) (4)-0232 V116: Immunogenicity In Adult (b) (4) Monkeys Amendment 2

The (b) (4) conducted two nonclinical pharmacology studies in adult (b) (4) monkeys (V116 ARM-1 and V116 ARM-3). In study ARM-1, they administered V116 intramuscularly at Days 0, 28 and 56, and collected blood samples at multiple time points to analyze serotype-specific IgG titers in ECL and functional antibodies in MOPA. The study showed that V116 was immunogenic and generated functional antibodies in adult monkeys. In study ARM-3, they compared the immunogenicity of V116 to other pneumococcal vaccines (V114, PCV13, and PPSV23). For shared serotypes, V116 had comparable immunogenicity to all three comparator vaccines.

PD003 (b) (4)-0233 V116: Immunogenicity In Mice (Msd Study Ms-6) Amendment 1

Merck conducted the nonclinical pharmacology study MS-6 in (b) (4) mice to compare the serotype-specific IgG titers elicited by two lots of V116: EIT-1 (002H001) and EIT-2 (002H002). The study demonstrated that both lots of V116 elicited comparable IgG antibody responses.

PD004 (b) (4)-0229 V116: Evaluation of T Cell Response In (b) (4) Mice Following Immunization With V116

In study MS-20, Merck immunized (b) (4) mice intramuscularly with V116 at Days 0, 28, and 56, and collected spleens at Day 70 to assess CRM197-specific T cell responses by (b) (4) and an in vitro stimulation immunoassay. In the in vitro stimulation immunoassay, they incubated splenocytes with CRM197 peptides for 48 hours, and determined several cytokine concentrations (IFN γ , IL-1 β , IL-2, IL-4, IL-5, IL-10, IL-12p70, TNF α , and KC-GRO) in culture medium by (b) (4) kit. The study demonstrated that V116 elicited CRM197-specific T cell responses in (b) (4) mice.

Module 5

Serology Assays

Merck performed the multiplexed opsonophagocytic killing assay (MOPA), (b) (4) assay, and the pneumococcal electrochemiluminescence (Pn-ECL) assay to assess clinical samples to support the immunogenicity of V116.

Information Request

On **January 30, 2024**, we sent an Information Request (CBER Comment 1) requesting that Merck provide the versions of the MOPA and Pn-ECL validation reports they used when analyzing the clinical studies reported in this BLA, because the versions provided under the BLA were not the most up-to-date versions included in the IND (submitted to IND 19316.80 and 19316.93). We also requested that, if

they used the updated reports included in the IND, that they provide them under the BLA.

On February 8, 2024 (STN 125814/0.10, Sequence Number 0011), Merck confirmed that they analyzed the sera from the clinical studies using MOPA and Pn-ECL following the updated validation reports submitted in IND 19316.80 and 19316.93. In response to the IR, the applicant submitted the updated lower limits of quantitation (LLOQs) of MOPA (08HQWB, Method Validation Statistical Report Amendment 1). However, they did not submit the updated information regarding the extravariability of Pn-ECL (see pages 125–127 of the memo). We sent an additional information request for this information (see below under the Pn-ECL section).

The Multiplexed Opsonophagocytic Killing Assay (MOPA)

At the request of Merck Research Laboratory, (b) (4) developed and conducted MOPA to quantitate functional antibodies against *S. pneumoniae* serotypes 3, 6A, (b) (4), 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 20B, 22F, 23A, 23B, 24F, 31, 33F and 35B.

Please note that I reviewed the MOPA SOP and validation reports under IND 19316/41, IND 19316/80, and IND 19316/93. Please refer to my memos under these IND submissions for additional details of the assay validations.

MOPA SOP (07ZSG3, VSDVAC 71 Version 2.00)

The MOPA is used to measure opsonophagocytic activity (OPA) of antibodies in human serum. Briefly, (b) (4)

[REDACTED]

MOPA Fit-for-Purpose (FFP) Summary Report (07ZRTV, VSDVAC 71 Version 0.00)

(b) (4) conducted a FFP assessment using the draft SOP VSDVAC 71 v0.0 to establish system suitability criteria and preliminary limits of quantitation (LOQ). They first selected (b) (4) assay quality control sera (QCS) and samples for FFP assessment after screening (b) (4) samples in (b) (4) independent runs. The selected QCS and

samples were used for conducting (b) (4) experiments in the FFP assessment (I: Ruggedness, Precision, Relative Accuracy and Dilutional Linearity, II: Specificity, and III: Matrix Interference).

(b) (4) established the QCS limits based on the OPA titers obtained during the FFP assessment. The following performance parameters were assessed, and all met the acceptance criteria: Ruggedness, Precision, Relative Accuracy and Dilutional Linearity, Specificity, and Matrix Interference. The assay LLOQ and upper LOQ (ULOQ) for each serotype were estimated from the precision and relative accuracy analyses. The LOQs were further evaluated during the assay validation and are reviewed below and under IND 19316/41 and 19316/80. Merck has provided adequate demonstration the MOPA method has been optimized for its intended use.

For a more detailed review of the FFP assessment please refer to my review memo for IND 19316/41.

MOPA Method Validation

I reviewed the following documents in this section:

- MOPA Method Validation Plan (07ZZZG, VSDVAC_71_V1-00_VP)
- Method Validation Plan Addendum (08F39T, VSDVAC_71_V1-00_VP_Adden1)
- Method Validation Plan Addendum (08F39W, VSDVAC_71_V1-00_VP_Adden2)
- Method Validation Plan Addendum (08F39X, VSDVAC_71_V1-00_VP_Adden3)
- Method Validation Statistical Report (07ZRHF, Version 1.0)
- Method Validation Addendum 1 Statistical Report (084RDP, Version 1.0)
- Method Validation Addendum 2 Statistical Report (084RDQ, Version 1.0)
- V116 MOPA Method Validation Addendum 3 Statistical Report (0868RM, Version 1.0)

(b) (4) designed the MOPA validation experiments to verify the performance parameters determined during the FFP evaluation. The following parameters were evaluated: Ruggedness, Precision, Relative accuracy/Dilutional linearity, LLOQ and ULOQ, Analytical specificity, and Matrix interference. Ruggedness was also evaluated in the validation study.

I reviewed the validation reports extensively under IND amendments 19316/41 and 19316/80. Please refer to those memos for details. Below I have included summaries for each validation parameter.

Method Performance Evaluation

(b) (4)

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

(b) (4)

[Redacted]

[Redacted]

MOPA Summary:

(b) (4) assessed the MOPA assay method in terms of the following performance parameters: Ruggedness, precision, relative accuracy/dilutional linearity, LLOQ and ULOQ, analytical specificity, and matrix interference. All performance parameters met the acceptance criteria. (b) (4) adequately validated the MOPA for its intended use of generating data for clinical studies with OPA GMTs at day 30 post-vaccination, the GM fold-rise of OPA GMTs from baseline (day 1) to day 30 post-vaccination, and the percentage of the population with ≥ 4 -fold rise in OPA GMTs from baseline to day 30 post-vaccination.

(b) (4)

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

The Pneumococcal Electrochemiluminescence (Pn-ECL) Assay

At the request of Merck, PPD developed and conducted the Pn-ECL assay to quantitate serum IgG titers of clinical samples for secondary endpoints in the phase 3 studies. This assay was used for evaluation of secondary endpoints in phase 3 clinical studies.

Pn-ECL SOP (07ZSG2, VSDVAC 50 Version 3.00)

The ECL method measures anti-pneumococcal Ps (PnPs) antibodies against serotypes 3, 6A, (b) (4), 7F, 8, 9N, 10A, 11A, 12F, 15A, deOAc15B (15C), 15B, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B. The Pn-ECL assay is based on (b) (4)

The SOP, including validity criteria, was reviewed extensively under IND 19316/41.

(b) (4) developed a reference standard called Merck Pneumococcal Reference Serum Standard, or MPRSS-01, by (b) (4)

(b) (4)

Pn-ECL Method Validation Plan

I reviewed the following documents in this section:

- Pn-ECL Method Validation plan (07ZZZF, VSDVAC_50_V2-00_VP)
- Method Validation Plan Addendum 1 (08DXMD, VSDVAC_50_V3-00_VP_Adden 1)

(b) (4) validation plan included assessments of performance parameters (Ruggedness and Precision, Relative Accuracy, Selectivity and LOD, Specificity, Dilutional Linearity, LOQs). Their validation plan was acceptable. For a detailed review please refer to my memo under IND 19316/41.

Pn-ECL Reference Standard Calibration Statistical Report (083QTG, Version 1.0)

In order to support the Merck Pneumococcal conjugate programs that include pneumococcal serotypes for which there are no antibody concentration assignments in the (b) (4) reference standard, (b) (4) developed human reference standard MPRSS-01, which contains antibodies to (b) (4) pneumococcal serotypes (b) (4) serotypes having an established assignment for (b) (4), and (b) (4) serotypes targeted by V116 but not having an established assignment for (b) (4) for internal use in vaccine immunogenicity studies.

(b) (4) used (b) (4) approaches to calibrate MPRSS-01 to (b) (4). In (b) (4)

For the (b) (4) serotypes having an established IgG assignment for (b) (4) assigned the corresponding antibody concentrations in MPRSS-01 via the direct calibration of MPRSS-01 to (b) (4) in the Pn-ECL using a similar approach when (b) (4) was calibrated to the original human anti-pneumococcal standard reference Lot (b) (4). Parallel line analyses using a four-parameter logistic regression function was used to test the adequacy of (b) (4)

To calibrate the (b) (4) serotypes not having an established IgG assignment for (b) (4) assigned the corresponding antibody concentration in MPRSS-01 using a (b) (4) step process.

(b) (4)

(b) (4)

After applying the new concentration assignment to the (b) (4) and MPRSS-01 reference standards, (b) (4) assessed each of the standards by comparing the QCS antibody concentrations determined from both the MPRSS-01 and (b) (4) reference standards. All results, except for one set of results, were within (b) (4)-fold when calculated with each of the standards. (b) (4) considered one set an outlier and excluded this set from analysis. Results on page 136 of the report clearly support (b) (4) conclusion that those results were aberrant and should be excluded.

The assignment of antibody concentrations to all serotypes in V116 in reference serum MPRSS-01 was appropriately determined.

Pn-ECL Method Validation

I reviewed the following documents in this section:

- Pn-ECL Method Validation Statistical Report (07ZRHD, Version 1.0)
- Method Validation Addendum 1 Statistical Report (08DXMF, Version 1.0)

To validate the Pn-ECL assay for use in detecting serotype-specific total IgG against PnPs in serum samples from Phase 3 clinical testing, (b) (4) performed (b) (4) experiments to evaluate the characteristic parameters (I: Ruggedness and Precision, II: Relative Accuracy, III: Selectivity and LOD, IV: Specificity, and V: Dilutional Linearity) of the assay. The studies were reviewed extensively in my memo under IND 19316/41. Below I have included a summary of each parameter.

(b) (4)

(b) (4)

Information Request

On **May 3, 2024**, we sent the following IR regarding the EXV rate. Merck responded on May 8, 2024 (STN 125814/0.29, Sequence Number 0043).

CBER Comment 1: *On 18 October 2023, you submitted to BLA 125814 VSDVAC 50: Method Validation Statistical Report Version 1.0 RRTB3: Validation of an ECL Method (V116) for the Detection of Antibodies to Pneumococcal Polysaccharide Serotypes 3, 6A, 7F, deOAc15B, 19A, 22F, 23A, 33F ((b) (4)), 8, 9N, 10A, 11A, 12F, 15B, 17F, 20A ((b) (4)), and (b) (4), 15A, 16F, 23B, 24F, 31, 35B ((b) (4)) in Human Serum. In this validation report, you indicated that you would monitor the extravariability (EXV) of the assay during Phase 3 clinical testing and modify and set more liberal EXV criteria. This validation report is the same version of the ECL Method Validation Statistical Report in IND 19316, submitted in amendment 41 on 29 March 2022. In our IR to IND 19316, dated 29 July 2022, we recommended that you should not modify the EXV criterion after validation as modifying the EXV criterion after validation could affect the validation conclusion. You responded to the IR in IND 19316 amendment 80 on 26 September 2022, and indicated that you would not modify the EXV criterion after validation. For consistency purposes, please submit to BLA 125814 the latest version of the ECL Method Validation Statistical Report containing this update. Also please submit the EXV rates in V116 Phase 3 clinical studies.*

Response: Merck indicated that they did not change the EXV criterion since validation and that they applied the EXV limits established during V116 Pn-ECL validation for the V116 Phase 3 clinical testing; thus they did not need to provide an updated report. They demonstrated that the average EXV rate was (b) (4) for the V116 Phase 3 clinical studies. Their updated approach is adequate.

Precision

(b) (4)

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

(b) (4)

Pn-ECL Summary:

(b) (4) assessed the Pn-ECL method in terms of performance parameters (Precision, LOQs, Assay Ruggedness, Selectivity, Specificity and Dilutional Linearity). All performance parameters met their respective acceptance criteria. (b) (4) established their standard curve using reference standard MPRSS-01, which they calibrated to the (b) (4). The high EXV rates observed during the validation were not observed in the V116 Phase 3 clinical studies. (b) (4) adequately validated the Pn-ECL for its intended use of generating data for clinical studies with IgG GM concentrations (GMCs) at day 30 post-vaccination, the GM fold-rise, and the percentage of population with ≥ 4 -fold rise in IgG GMCs from baseline to day 30 post-vaccination.

Assay Stability Information Request

On **April 23, 2024**, we sent an Information Request requesting that Merck provide data demonstrating the stability of the MOPA and the Pn-ECL assays from validation throughout their use in the testing of samples from the Phase 3 clinical studies.

On April 30, 2024 (STN 125814/0.27, Sequence Number 0034), Merck provided assay trending data for the MOPA (08KR7W) and the Pn-ECL (08KR7V). These data demonstrate that both the MOPA and the Pn-ECL were stable during the period of testing samples from the Phase 3 clinical studies. Their response was adequate.

The V116 serotype-specific urinary antigen detection (SSUAD) assay and the pneumococcal antigen detection (PAD) assay

The SSUAD and the PAD are high-throughput, multiplex assays for the measurement of serotype-specific PnPs of *S. pneumoniae* in adult urine and blood, respectively. Merck is currently developing these assays aiming to test samples from the real-world evidence (RWE) studies they intend to utilize to support traditional approval for their pneumonia indication after accelerated approval under this original BLA. In their

proposal, Merck indicated that these assays would not distinguish between serotypes (b) (4), or between (b) (4).

Information Request

On **February 1, 2024**, we sent an IR requesting that Merck provide the validation reports for SSUAD and PAD assays to see if these assays would be able to distinguish the cross-reactive serotypes ((b) (4)) from the vaccine serotypes ((b) (4)) because the cross-reactivity between these serotypes will likely lead to misidentification of the cross-reactive serotypes as vaccine serotypes in these assays (CBER Comment 1). On February 15, 2024 (STN 125814/0.13, Sequence Number 0014), Merck submitted an amendment in which they estimate that the impact of these assays on the overall vaccine effectiveness (VE) by misidentification of cross-reactive serotype (b) (4) as vaccine serotype (b) (4) should be a very minimal due to the low-prevalence of serotype (b) (4), citing the community-acquired pneumonia (CAP) study of PCV13. In addition, Merck is exploring alternate methodologies enabling to distinguish cross-reactive serotype (b) (4) from vaccine serotype (b) (4). They indicated they will submit the validation packages by the second quarter of 2025.

On March 8, 2024 (STN 125814/0.14, Sequence Number 0015), Merck submitted developmental data to support the V116 SSUAD's specificity to distinguish cross-reactive serotype (b) (4) from vaccine serotype (b) (4). They assessed the specificity of the assay by (b) (4)

In order to accurately review the developmental data, we sent another IR on **May 3, 2024**, requesting that Merck provide information on the quantity of the polysaccharides they used to (b) (4) (CBER Comment 1). On May 8, 2024 (STN 125814/0.29, Sequence Number 0043), Merck submitted the polysaccharide (b) (4) for each serotype and the SSUAD SOP (089BLC, Version 7.0). Urine samples were (b) (4) ration of the ULOQ for each serotype. However, they did not describe how they determined LOQs of this assay in the document they submitted. Also, for 17 out of 21 serotypes (including (b) (4)), the measured polysaccharide concentrations were (b) (4).

In future communications under IND 19316, we will ask Merck to describe the LOQ determination method and to clarify how the (b) (4). Since the SSUAD will be used in future RWE studies and the comments we will communicate will likely not disqualify the assay, these comments do not prevent the approval of this BLA. The applicant can submit the responses to these clarifications as amendments to the IND after the approval of the BLA.

Information Request

On **May 29, 2024**, in conjunction with the clinical review team, we sent an IR informing Merck that CBER will include in the Approval letter milestones regarding

the submission date of the SSUAD and PAD validation protocols and reports to ensure that we can complete our review before they initiate the evaluation of samples from the RWE test-negative design (TND) studies. This IR stemmed from internal CBER discussion wherein concerns were raised regarding the applicant moving forward with their confirmatory studies without fully validated assays that they will use to establish efficacy.

In their response submitted on May 31, 2024 (STN 125814/0.33, Sequence Number 0069), Merck indicated that they intend to commit to May 30, 2025, for submission of the validation packages, in line with their previously communicated timeline of Q2 2025 (STN 125814/0.13, Sequence Number 0014). Merck also indicated that they planned to submit the validation protocols by November 1, 2024.

We do not object to the proposed dates for submission of validation protocols (November 1, 2024) and for submission of the validation reports (May 30, 2025).

Clinical Studies

Merck conducted four Phase 3 studies and one Phase 1/2 study to evaluate V116 vaccine efficacy in adults ≥ 18 years of age.

- Phase 3 studies: V116-003 (Pivotal, ≥ 18 years), V116-004 (Lot consistency), V116-005 (Concomitant), and V116-006 (≥ 50 years)
- Phase 1/2 study: V116-001

In all clinical studies, the primary immunogenicity objectives utilized the MOPA to measure pneumococcal antibody function as primary endpoints. In addition, Merck used the pneumococcal electrochemiluminescence (Pn-ECL) assay to assess IgG responses for secondary objectives (geometric mean IgG concentrations). As described above, the validation reports and additional documentation are sufficient to support the adequate performance of the assays. No aberrant or unusual data were noted in the clinical study reports that would indicate performance issues. This section summarizes the serology-related endpoints from these clinical studies. For full reviews of these studies, including descriptions of study results for each endpoint, please refer to the clinical review team's memo.

Phase 3 studies

V116-003 (Noninferiority/Superiority Study)

Merck evaluated the safety, tolerability, and immunogenicity of V116 in pneumococcal vaccine-naïve adults ≥ 18 years of age by comparing the responses to those in participants immunized with PCV20. Merck enrolled participants ≥ 50 years of age in cohort 1 and participants 18 to 49 years of age in cohort 2. They conducted the pivotal analysis in cohort 1. Participants received a single dose of V116 or PCV20. Merck conducted serum Pn-ECL and MOPA analyses at day 30 post-vaccination. Merck assessed immunological noninferiority for 10 common serotypes (3, 6A, 7F, 8, 10A, 11A, 12F, 19A, 22F, and 33F) contained in both V116

and PCV20 and immunological superiority for 11 unique serotypes (9N, 15A, 15C, 16F, 17F, 20A, 23A, 23B, 24F, 31, and 35B) contained in V116 but not in PCV20.

Primary endpoints:

- Noninferiority for each of the 10 common serotypes, defined as the lower bound of the two-sided 95% confidence interval (CI) of the OPA geometric mean titer (GMT) ratio [V116/PCV20] >0.5.
- Superiority each of the 11 unique serotypes, defined as the lower bound of the two-sided 95% CI of the OPA GMT ratio [V116/PCV20] >2.0.
- Superiority of V116 to PCV20 based on the proportions of participants with a ≥ 4 -fold rise in OPA titers from baseline (day 1) to day 30 post-vaccination for each of the 11 unique serotypes. Merck declared superiority if the lower bound of 95% CI of the percentage point difference [V116 - PCV20] in the percentage of participants with a ≥ 4 -fold rise in OPA titers from baseline (day 1) to day 30 post-vaccination was >0.1 [10 percentage points].
- Noninferiority (immunobridging) of cohort 2 to cohort 1. The success criterion for immunobridging was defined as the lower bound of the 2-sided 95% CI of the OPA GMT ratio [cohort 2/ cohort 1] >0.5.

Secondary endpoints:

- IgG geometric mean concentration (GMC) at day 30 post-vaccination between V116 and PCV20 for all 21 serotypes without a success criterion.
- Evaluation of cross-reactive immune responses to serotypes 6C and 15B:
 - Merck set forth a statistical success criterion if >50% of participants' OPA GMT lower bound of 95% CIs reached a ≥ 4 -fold rise from baseline (day 1) to day 30 post-vaccination.
 - Evaluated OPA GMT ratio [cohort 2/cohort 1] for serotypes 6C and 15B to immunobridge between cohort 2 and cohort 1 by the same immunobridging criterion used for the primary endpoint.

Information Request

We sent on the following IR on **March 11, 2024**, in conjunction with the clinical review team. Merck responded on March 13, 2024 (STN 125814/0.15, Sequence Number 0016).

CBER Comment: *You are seeking an IPD indication for the cross-reactive serotype 15B based on secondary endpoints assessed in Phase 3 study V116-003. We do not concur. It is not adequate to include a serotype in the indication without the assessment of responses as a primary endpoint. All serotypes included in the indication should be subjected to the primary objective criteria . We consider serotype 15B a common serotype as PCV20 contains serotype 15B. Please provide an analysis of OPA responses to serotype 15B using the non-inferiority criterion established for a primary endpoint.*

Response: Merck submitted the results of the non-inferiority assessment in comparison to PCV20 and the immunobridging assessment between the two age groups. V116 met the success criteria for both assessments.

We defer to the clinical review team for acceptability of this conclusion.

V116-004 (Lot-to-Lot Consistency Study)

Merck tested consistency in immunogenicity between three V116 vaccine lots. They administered a single dose of either V116 Lot 1, V116 Lot 2, V116 Lot 3, or PPSV23 to pneumococcal vaccine-naïve adults 18 to 49 years of age and assessed OPA GMTs at day 30 post-vaccination for all 21 serotypes contained in V116.

Primary endpoint:

- Lot equivalence for all serotypes, defined as the bounds of the 95% CI of the serotype-specific OPA GMT ratios between any two lots (i.e., Lot 1/Lot 2, Lot 1/Lot 3, or Lot 2/Lot 3) were within 0.5 to 2.0.

Secondary endpoints:

- Compared OPA GMTs and IgG GMCs at day 30 post-vaccination between the combination of the three V116 vaccine lots and PPSV23 for the 12 serotypes (3, 7F, 8, 9N, 10A, 11A, 12F, 17F, 19A, 20A, 22F, and 33F) contained in both V116 and PPSV23 and the nine new serotypes in V116 (6A, 15A, 15C, 16F, 23A, 23B, 24F, 31, and 35B).
- Evaluated GMFRs and the percentage of participants with a ≥ 4 -fold rise in OPA titers and IgG GMCs from day 1 to day 30 post-vaccination for all 21 serotypes.

V116-006 (Immunogenicity in Pneumococcal Vaccine-Experienced Adults ≥ 50 Years of Age)

Merck evaluated the safety, tolerability, and immunogenicity of V116 in adults ≥ 50 years of age who had received pneumococcal vaccines ≥ 1 year prior to enrollment. Merck allocated participants into three groups: participants with prior PPSV23 vaccination history (cohort 1), with prior PCV13 vaccination history (cohort 2), and with prior PCV13+PPSV23, PCV15+PPSV23, PPSV23+PCV13, PCV15, or PCV20 vaccination history (cohort 3). They administered a single dose of either V116 or PCV15 to cohort 1, a single dose of either V116 or PPSV23 to cohort 2, and a single dose of V116 to cohort 3. Merck provided descriptive summaries without a statistical hypothesis.

Primary endpoint:

- Evaluate serotype-specific OPA GMTs at day 30 post-vaccination for the 21 serotypes contained in V116 in comparison with comparators.

Secondary endpoints:

- Evaluate serotype-specific IgG GMCs between V116 and the comparator for 21 vaccine serotypes in V116 at day 30 post-vaccination.

- Evaluate serotype-specific geometric mean fold rise (GMFR) and proportion of subjects with a ≥ 4 -fold increase from baseline to 30 days post-vaccination for both OPA and IgG responses for the 21 serotypes contained in V116.

In their exploratory objective, Merck assessed OPA and IgG responses in all three cohorts at day 30 post-vaccination for cross-reactive serotypes 6C and 15B in all three cohorts.

V116-005 (Co-Administration with Influenza Vaccine)

Merck evaluated the safety, tolerability, and immunogenicity of V116 in adults ≥ 50 years of age who concomitantly received quadrivalent influenza vaccine (QIV). Merck allocated participants into two groups equally in terms of age distribution and previous pneumococcal vaccination history: concomitant group and sequential group. In the concomitant group, Merck administered V116 and QIV to participants at day 1 and collected blood samples at day 30. In the sequential group, Merck administered QIV to participants at day 1 followed by V116 vaccination at day 30 and collected blood samples at day 59 (i.e., day 30 after V116 vaccination). Merck assessed the serotype-specific OPA GMTs at day 30 post-vaccination for V116 and the strain-specific hemagglutination inhibition (HAI) GMTs for QIV. For review of the HAI assay and endpoints, we defer to the virology reviewer.

Primary endpoint:

- Compare serotype-specific OPA GMTs 30 days post-vaccination with V116 administered with QIV vs. V116 administered sequentially with QIV. Noninferiority was defined for each of the 21 serotypes if the lower bound of the two-sided 95% CI of the OPA GMT ratio [concomitant/sequential] was >0.5 .

Secondary endpoints:

- Evaluate IgG GMCs at day 30 after V116 vaccination for subjects receiving both vaccines concomitantly vs. sequentially.
- Evaluate OPA and IgG GMFRs from day 1 to day 30 after V116 vaccination, and the proportion of participants with a ≥ 4 -fold rise in OPA GMTs and IgG GMCs from day 1 to day 30 after V116 vaccination for each of the 21 serotypes.

In additional exploratory endpoints, Merck assessed OPA and IgG responses for cross-reactive serotypes 6C and 15B.

Phase 1/2 Studies

V116-001 (Noninferiority/Superiority Study)

Merck evaluated the safety, tolerability, and immunogenicity of V116 in pneumococcal vaccine-naïve adults ≥ 18 years of age in comparison with PPSV23. Merck tested participants 18 to 49 years of age in Phase 1 portion and ≥ 50 years of age in Phase 2 portion.

Phase 1 Study

Merck evaluated two dose strengths of V116: pPCV-1 (2 µg of each polysaccharide per conjugate in 0.5 mL) and pPCV-2 (4 µg of each polysaccharide per conjugate in 1.0 mL). They administered a single dose of pPCV-1, pPCV-2 or PPSV23 to participants at day 1 and collected blood samples at day 30 post-vaccination. Merck conducted the analysis of safety as primary endpoint (no safety concerns were identified) and immunogenicity assessments (without success criteria) as secondary endpoints.

Phase 2 Study

Merck administered a single dose of V116 or PPSV23 to participants at day 1 and collected blood samples for immunogenicity assessments at day 30 post-vaccination. They assessed immunological noninferiority for 12 serotypes contained in both V116 and PPSV23 (3, 7F, 8, 9N, 10A, 11A, 12F, 17F, 19A, 20A, 22F, and 33F), and immunological superiority for nine serotypes contained in V116 but not in PPSV23 (6A, 15A, 15C, 16F, 23A, 23B, 24F, 31, and 35B). Merck also assessed as an exploratory analysis the immunogenicity of V116 for three cross-reactive serotypes (6C, 15B, and 20B) without a success criterion.

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

Merck adequately validated the MOPA, ^{(b) (4)}, and Pn-ECL assays for their intended purposes to evaluate primary and secondary clinical endpoints in Merck's clinical studies for V116. They also provided data to support that the MOPA and Pn-ECL assays performed consistently during the clinical testing period, through the Phase 3 studies. I found no deficiencies. The SSUAD and PAD assays will be further reviewed under future submissions to the IND as development continues and their current state of development does not prevent the approval of this BLA.