

CBER CMC BLA Review Memorandum

BLA STN 125741

**Pneumococcal 15-valent Conjugate Vaccine [CRM₁₉₇ Protein], (b) (4)
VAXNEUVANCE**

**John Cipollo Ph.D. /Laboratory of Bacterial Polysaccharides/Division of Bacterial
Parasitic and Allergenic Products/Office of Vaccines Research and Review**

**James E. Keller Ph.D. /Laboratory of Respiratory and Special Pathogens/Division
of Bacterial Parasitic and Allergenic Products/Office of Vaccines Research and
Review**

**Mustafa Akkoyunlu MD, Ph.D. /Laboratory of Bacterial Polysaccharides/Division
of Bacterial Parasitic and Allergenic Products/Office of Vaccines Research and
Review**

1. **BLA#:** STN 125741

2. **APPLICANT NAME AND LICENSE NUMBER**

Merck Sharp and Dohme Corporation

3. **PRODUCT NAME/PRODUCT TYPE**

VAXNEUVANCE™

Pneumococcal 15-valent Conjugate Vaccine [CRM197 Protein], (b) (4)

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

- a. Vaccine
- b. Sterile Suspension for Injection supplied in a stoppered syringe with a plunger rod.
- c. The Drug Product provides a total of (b) (4) of total Pneumococcal Polysaccharide (PnPs) Antigens conjugated to approximately (b) (4) of CRM₁₉₇ as Monovalent Bulk Conjugate (MBC) (b) (4) Potency is measured by (b) (4) assay targeting total and conjugated saccharide.
- d. Intramuscular injection
- e. Prevention of Pneumococcal Disease (Serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F) in adults 18 years of age and older.

5. **MAJOR MILESTONES**

- Acknowledgement Letter – 3 December 2020
- First Committee Meeting – 10 December 2020
- Filing Meeting – 3 January 2021
- Mid-Cycle Meeting – 3 March 2021
- Exclusivity claim received 19 November 2020, the date of first approval for the reference product will be granted 18 July 2021 with an expiry date 18 July 2033. A 351(k) product may be submitted for review 18 July 2025.
- Late Cycle Meeting 12 May 2021
- PDUFA Action Due Date – 18 July 2021

6. **CMC/QUALITY REVIEW TEAM**

Reviewer/Affiliation	Section/Subject Matter
John Cipollo, OVRR/DBPAP/LBP	Exclusivity Request (1.3.5.3) Drug Substance and Polysaccharide Intermediate (2.3.1 through 2.3.R, 3.2.S.1 through 3.2.S.7.3, 3.2.P.1 through 3.2.P.8.3, 3.2.A.2, 3.2.A.3, 3.2.R relevant to Drug Substance Polysaccharide Intermediate and Drug Product

Reviewer/Affiliation	Section/Subject Matter
James Keller, OVR/DBPAP/LRSP	Drug Substance Intermediate Manufacture of CRM ₁₉₇ 2.3.S, 3.2.S.2.1 through 3.2.S.2.6 and 3.2.S.3, 3.2.S.4, 3.2.S.5, 3.2.S.2.6, 3.2.S.7, and parts of 3.2.R relevant to CRM ₁₉₇ manufacture.
Mustafa Akkoyunlu, OVR/DBPAP/LBP	MOPA and ECL assays used in the efficacy evaluation of V114 in clinical studies under 5.3.1.4 "Bioanalytical and Analytical Methods for Human Studies." Reports of clinical studies pertinent to the claimed indication under section 5.3.5.1. (b) (4) assay related submissions under section 5.3.5.4 "Other Study Reports." Animal studies to assess the immunogenicity of V114 under 4.2.1 "Pharmacology" and 4.2.3 "Toxicology" sections.

7. INTER-CENTER CONSULTS REQUESTED

No inter-center consults were requested

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
10/21/2020	STN 125741/0	Rolling Submission #1
11/17/2020	STN 125741/0.1	Rolling Submission #2
11/18/2020	STN 125741/0.2	(Proprietary name)
1/25/2021	STN 125741/0.4	(Response to 1/11/2021 CMC and serology IR #2) update 3.2.S.2.2, 3.2.S.2.5 for (b) (4) validation data. ECL and MOPA related SOP and qualification reports were submitted. Responses were acceptable.
1/27/2021	STN 125741/0.6	Response to 1/11/2021 & 1/25/2021 CMC IR #2 EK: CRM ₁₉₇ Comments 4, 5, and 6. Responses were acceptable. JC: Comments 5 and 11. Responses were acceptable.

Date Received	Submission	Comments/ Status
2/9/2021	STN 125741/0.7	Unsolicited update to stability data and analytical methods
2/10/2021	STN125741/0.8	Response to 2/1/2021 DBSQC CMC IR #3
02/18/2021	STN 125741/0.10	Response to 02/05/2021 CMC IR #4
02/18/2021	STN 125741/0.11	Response to 02/09/2021 CMC IR #6
02/25/2021	STN 125741/0.14	Response to 02/17/2021 CMC IR #8
02/26/2021	STN 125741/0.15	Response to 02/10/2021 serology IR #7 related to ECL and MOPA assay stability.
03/10/2021	STN 125741/0.18	Response to IR #9 regarding request for product exclusivity
03/12/2021	STN 125741/0.19	Response to 03/05/2021 CMC IR #10
03/26/2021	STN 125741/0.23	Response to 3/19/2021 IR #13 related to serology (b)(4) assay V1 qualification report and CMC
03/24/2021	STN 125741/0.21	Response to 03/12/2021 CMC IR #12
04/02/2021	STN 125741/0.24	Response to CMC IR #14 sent 03/26/21
04/07/2021	STN 125741/0.25	Response to CMC IR #8 sent 02/17/2021
04/12/2021	STN 125741/0.27	Response to CMC IR #15 sent on 04/02/2021
04/16/2021	STN 125741/0.28	Response to CMC IR #16 sent on 04/09/2021
04/23/2021	STN 125741/0.29	Response to IR #17 sent on 04/16/2021.
04/30/2021	STN 125741/0.31	Response to IRS #17 & 18 sent on 04/16/2021 and 04/23/2021.
05/03/2021	STN 125741/0.32	Response to IR #19 sent on 04/26/2021 re LRP

Date Received	Submission	Comments/ Status
05/21/2021	STN 125741/0.34	Response to IR # 21 sent on 05/14/2021 re LRP

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)	Authorization	yes	Authorization of HAI procedure. Reference is made to use of the assay in study protocol V114-021.
DMF (b) (4)	(b) (4)	Authorization	yes	Authorization to incorporate by reference information regarding (b) (4) in master file (b) (4)
DMF (b) (4)	(b) (4)	Authorization	yes	Authorization for FDA to review information pertaining to (b) (4) Glass Prefillable Syringe
DMF (b) (4)	(b) (4)	Authorization	yes	authorizes Merck and Co., Inc. to incorporate by reference information regarding (b) (4)
DMF (b) (4)	(b) (4)	Authorization	yes	authorizes FDA to reference Type V Drug Master File
Not provided	Merck Sharp and Dohme	Authorization	yes	Merck is providing authorization to cross reference BB-MF (b) (4) in its entirety, in support of BLA 125741.

10. REVIEWER SUMMARY AND RECOMMENDATION
A. EXECUTIVE SUMMARY

Merck is seeking licensure of a 15-valent pneumococcal conjugate vaccine, Vaxneuvance. Active ingredients consist of fifteen pneumococcal capsular polysaccharides linked to the carrier protein CRM₁₉₇. The polysaccharides are derived from the capsules of *Streptococcus pneumoniae* Serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F. Each polysaccharide is purified, rendered the appropriate size, and activated. The CRM₁₉₇ carrier protein is an inactivated form of the Diphtheria toxin recombinantly expressed in *Pseudomonas fluorescens*. The polysaccharides are activated via (b) (4) oxidation process. These active groups are then utilized in subsequent reductive amination process to link the polysaccharides to the carrier protein's (b) (4) reductive amination.

The polysaccharides are produced at the (b) (4) manufacturing site, at which pneumococcal polysaccharides are already being manufactured for (b) (4). The CRM₁₉₇ carrier protein is produced at (b) (4). The monovalent bulk conjugates are produced at the (b) (4). The drug product (DP) is formulated and filled at the (b) (4) site in (b) (4).

The principles of quality-by-design detailed in ICH Q8 (R2) and the Failure Mode Effects Analysis (FMEA) in ICH Q9, were used to evaluate the process parameters and establish the in-process attributes and parameter ranges for establishment of specifications. Critical Process Parameters (CPP) and Critical Quality Attributes (CQA) were established throughout the manufacturing process for intermediates, drug substance (DS) and DP manufacture. In Process controls (IPC) were established where appropriate. Key Process Attributes (KPA) and Key operating parameters (KOPs) were also established.

Release tests and in process tests were developed and validated as appropriate for all intermediates, DSs and DP. The testing panels adequately measure quality, 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 supported by validation data.

(b) (4) The company committed to develop these tests late in the IND stage and prior to BLA submission such that qualification activities would continue through to the end of 2020 and be implemented into the Formal Stability Study (FSS) and Process Performance Qualification (PPQ) batches by the end of 2022 as characterization tests. Both have been qualified, implemented as stated and ahead of schedule, and performing as expected. Through interactions with CBER, the tests will be established as release and stability tests and specifications assigned as appropriate.

The polysaccharides are stored at (b) (4). Stability data supports a (b) (4) for all serotypes. Stability data submitted for the CRM₁₉₇ intermediate stored (b) (4)

properties. Proposed shelf lives of serotypes 3, 4, 14, 22F and 33F are (b) (4). The proposed shelf life for serotypes 1, 6A, 9V, 18C, and 23F is (b) (4), and for serotypes 5, 6B, 7F, 19A, and 19F 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.

Vaccine-induced antibody binding to capsular polysaccharides and antibody-mediated opsonophagocytic killing of encapsulated *S. pneumoniae* is the main mechanism involved in the protection from pneumococcal disease. Therefore, the opsonophagocytic assay (OPA) is used to assess vaccine efficacy. The primary endpoint for assessing the efficacy of V114 is based on the demonstration of non-inferiority of V114 to licensed 13-valent pneumococcal conjugate vaccine (PCV13), Prevnar 13™ in OPA. In addition to OPA, serotype-specific IgG antibody responses for all 15 serotypes were measured using pneumococcal electrochemiluminescence (Pn ECL) assay as a secondary objective. The V114 vaccine contains the thirteen serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) included in the licensed vaccine Prevnar 13™ in addition to serotypes 22F and 33F that are not included in any currently licensed conjugate vaccine. A multiplexed OPA (MOPA) was used to support the clinical endpoints for the Phase 3 studies V114-016, V114-017, V114-018, V114-019, V114-020, and V114-021. The MOPA used to evaluate Phase 3 study samples was validated at (b) (4) and the clinical samples were tested at (b) (4). The Phase 2 study V114-007 samples were evaluated in a qualified MOPA (MOPA-4) at the (b) (4). The MOPA-4 was qualified at the (b) (4). The ECL (v2.0) used in the quantification of serotype specific IgG antibodies in Phase 3 study samples was validated and bridged to (b) (4) assay (b) (4). A qualified version of this ECL (v1.0) was used to measure serum IgG antibodies in study V114-007. Qualification of ECL and the testing of study V114-007 samples were done by (b) (4). Among the six Phase 3 studies, study V114-019 is the pivotal Phase 3 study where immunogenicity of V114 was compared to that of Prevnar 13™ in pneumococcal vaccine-naïve adults ≥50 years of age. The V114 vaccine met the primary and secondary efficacy objectives in study V114-019 and in all other clinical studies. The review prompted several information requests related to the standard operation procedure, validation, and assay quality control performance. Merck addressed these comments in amendments. Overall, the MOPA used in the evaluation of clinical endpoints for the Phase 3 studies, the MOPA-4 for

the evaluation of Phase 2 study V114-007 and the ECL assay used for the evaluation serum IgG antibody responses were adequate for their intended uses.

We recommend approval of STN 125741/0.

B. RECOMMENDATION

I. APPROVAL

We recommend approval.

II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
John Cipollo, Ph.D./OVRR/DBPAP/LBP	Concur	
James Keller, Ph.D./ OVRR/DBPAP/LRSP	Concur	
Mustafa Akkoyunlu, M.D., Ph.D./ OVRR/DBPAP/LBP	Concur	
Willie F. Vann, Ph.D./Supervisory Senior Research/DBPAP	Concur	
Jay E. Slater, M.D./Supervisory Medical Officer/DBPAP	Concur	

Review of CTD

Contents

1.1 ADMINISTRATIVE INFORMATION AND PRESCRIBING INFORMATION.....	2
3.2.S DRUG SUBSTANCE.....	5
3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties	5
3.2.S.2 Manufacture	5
3.2.S.2.1 Manufacturer(s)	5
3.2.S.2.2 Description of Manufacturing Process	6
3.2.S.2.3 Control of Materials	24
3.2.S.2.4 Controls of Critical Steps and Intermediates.....	32
3.2.S.2.5 Process Validation and/or Evaluation CRM ₁₉₇ :.....	44
3.2.S.2.6 Manufacturing Process Development	62
3.2.S.3 Characterization.....	75
3.2.S.3.1 Elucidation of Structure and Other Characteristics	75
3.2.S.3.2 Impurities.....	80
3.2.S.4 Control of Drug Substance.....	83
3.2.S.4.1 Specification(s) and 3.2.S.4.5 Justification of Specification(s).....	83
3.2.S.4.2 Analytical Procedures and 3.2.S.4.3 Validation of Analytical Procedures (CRM ₁₉₇)	88
3.2.S.4.4 Batch Analyses	89
3.2.S.5 Reference Standards or Materials	90
3.2.S.6 Container Closure System	92
3.2.S.7 Stability.....	95
3.2.S.7.1 Stability Summary and Conclusion and 3.2.S.7.3 Stability Data	96
3.2.S.7.2 Post-Approval Stability Protocol and Stability Commitment	99
3.2.P DRUG PRODUCT	100
3.2.P.1 Description and Composition of the Drug Product.....	100
3.2.P.2 Pharmaceutical Development	102
3.2.P.2.1 Components of the Drug Product	103
3.2.P.2.1.1 Drug Substance.....	102
3.2.P.2.1.2 Excipients.....	102
3.2.P.2.2 Drug Product	103
3.2.P.2.2.1 Formulation Development.....	104
3.2.P.2.2.2 Overages.....	107
3.2.P.2.2.3 Physicochemical and Biological Properties.....	107
3.2.P.2.3 Manufacturing Process Development	109
3.2.P.2.4 Container Closure System	110
3.2.P.2.5 Microbiological Attributes	112
3.2.P.2.6 Compatibility	112
3.2.P.3 Manufacture	113
3.2.P.3.1 Manufacturer(s).....	113
3.2.P.3.2 Batch Formula.....	113
3.2.P.3.3 Description of Manufacturing Process	114
3.2.P.3.4 Controls of Critical Steps and Intermediates.....	114
3.2.P.3.5 Process Validation and/or Evaluation.....	115

3.2.P.4 Control of Excipients	116
3.2.P.4.1 Specifications	116
3.2.P.4.2 and 3.2.P.4.3 Production Process for Aluminum Phosphate Adjuvant, Analytical Procedures and Validation of Analytical Procedures.....	116
3.2.P.4.4 Justification of Specifications.....	117
3.2.P.4.5 Excipients of Human or Animal Origin	117
3.2.P.4.6 Novel Excipient	117
3.2.P.5 Control of Drug Product.....	117
3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)	117
3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures.....	124
3.2.P.5.4 Batch Analyses	127
3.2.P.5.5 Characterization of Impurities.....	128
3.2.P.6 Reference Standards or Materials	128
3.2.P.7 Container Closure System	129
3.2.P.8 Stability	129
3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data	129
3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment	130
3.2.A APPENDICES	134
3.2.A.1 Facilities and Equipment	134
3.2.A.2 Adventitious Agents Safety Evaluation	134
3.2.A.3 Novel Excipients	134
3.2.R Regional Information (USA).....	134

Module 1

1.1 ADMINISTRATIVE INFORMATION AND PRESCRIBING INFORMATION

1.3.5.3 Exclusivity

(JC) The applicant filed a request for reference product exclusivity on 17 November 2020. Merck claimed there are no licensed biological products that are structurally related to the Vaxneuvance Pneumococcal 15-valent conjugate vaccine for which they or one of its affiliates, licensors, predecessors in interest, or related entities is the current or previous license holder. Merck does not believe that Pneumovax® is relevant to this claim. While it does contain fourteen of the fifteen serotypes in the Vaxneuvance vaccine none are conjugated to a carrier protein. To clarify the eligibility of the Vaxneuvance vaccine for the exclusivity claim the following IR was sent 24 February 2021.

Exclusivity Information Request

We are reviewing your BLA (STN 125741), received on November 17, 2020 for VAXNEUVANCE, a Pneumococcal 15-valent Conjugate Vaccine [CRM₁₉₇ Protein]

(b) (4) and have the following requests for additional information:

1. Please provide a list of all licensed biological products that are structurally related to the biological product that is the subject of the 351(a) application being considered. This list should include all products that share any of the same principal molecular structural features of the biological product being considered, but generally can be limited to products that affect the same molecular target.
2. Based on our advice above, please revise your exclusivity claim and submit a list of all licensed biological products that are structurally related and/or that share some of the same principal molecular structural features to the biological product that is the subject of the 351(a) application being considered. If your assessment results in the conclusion that no products that have the same molecular target or share some of the same principal molecular structural features have been licensed, please provide an adequate justification to support the assertion that there are no previously licensed products that are relevant for purposes of determining the date of first licensure. Of those licensed biological products identified in item 2 above, please identify the products for which you or one of your affiliates, including any licensors, predecessors in interest, successors in interest, or related entities are the current or previous license holder.
3. Please describe the structural differences between the biological product being considered and any products identified in item 3 above. For protein products, this should include, but is not limited to, changes in amino acid sequence, differences due to post-translational events, infidelity of translation or transcription, differences in glycosylation patterns or tertiary structure, and differences in biological activities.
4. Please provide evidence of the change in safety, purity, and/or potency between the proposed product and any products identified in item 3 above.

Response to the Exclusivity Information Request

A response was received 10 March 2021. Below is a summary of the company's response.

PNEUMOVAX®23, Prevnar® and Prevnar®13 were listed and described as FDA licensed products that are structurally related to Vaxneuvance. PNEUMOVAX23 is produced by Merck under BLA 101094. Both Prevnar® and Prevnar®13 are produced and licensed by Wyeth Pharmaceuticals, Inc.

2. Merck is the BLA holder for PNEUMOVAX23. Neither Merck nor any of its affiliates, including any licensor, predecessor in interest, successor in interest, or other related entity, is the current or previous license holder for either Prevnar® or Prevnar®13.

3. The company describes the differences between PNEUMOVAX23 and Vaxneuvance as in the number and composition of the serotypes included in the products.

Vaxneuvance contains 15 separate glycoconjugate antigens each containing a distinct polysaccharide coupled to the protein carrier CRM₁₉₇ whereas PNEUMOVAX23 polysaccharides are not conjugated to any protein carrier. Vaxneuvance contains aluminum phosphate adjuvant and PNEUMOVAX23 does not contain any adjuvant.

4. Merck cites “Draft Guidance for Industry, Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act (Aug. 2014)” On page 6 of the document it is stated that “FDA generally will presume that the modification has resulted in a change to the proposed product’s safety, purity, or potency if the sponsor of the proposed product demonstrates that it affects a different molecular target than the original product.” The company believes that this applies in this case. While some serotypes are shared between the two products, PNEUMOVAX23 and Vaxneuvance, the polysaccharides do not completely overlap. Moreover, PNEUMOVAX23 does not contain Serotype 6A whilst Vaxneuvance does. The drug products also differ in that PNEUMOVAX23 does not contain a carrier protein or adjuvant while Vaxneuvance does.

Immunogenicity afforded by the 15-valent conjugate formulation is superior versus the free polysaccharides as demonstrated in clinical studies in direct comparisons of the two vaccines ([Ref. 5.4: 03RBPX], [Ref. 5.4: 03QXDG], [Ref. 5.4: 03RS7G]).

Review of Response to the Exclusivity IR

Pneumovax23 contains twenty-three polysaccharides, many of which are contained in Vaxneuvance. However, the Pneumovax23 polysaccharides are not conjugated to a protein and therefore have a very different chemical structure than the Vaxneuvance polysaccharides. We agree that there are no currently licensed products in the USA produced by Merck other than Pneumovax®23 that are structurally related to the Vaxneuvance 15-valent vaccine.

Conjugation of the 15 Pneumococcal polysaccharides to the CRM₁₉₇ protein carrier and when combined with aluminum phosphate adjuvant leads to a stronger immune response against the serotypes contained therein and in common with Pneumovax23.

Determination of Exclusivity

The Vaxneuvance 15-valent polysaccharide conjugate vaccine is structurally and antigenically distinct from Pneumovax23 which has resulted in an increase immune response. Even though these two vaccines have the same sponsor, Vaxneuvance

qualifies to have its own date of first licensure due to the increased immune response and major differences in antigen structure. Thus, pursuant to Section 351(k)(7)(A), no approval of an application submitted under Section 351(k) for which Pneumococcal 15-valent Conjugate Vaccine [Diphtheria CRM₁₉₇ Protein] is the reference product can be made effective until 12 years after the date of licensure of Pneumococcal 15-valent Conjugate Vaccine [Diphtheria CRM₁₉₇ Protein]. In addition, pursuant to Section 351(k)(7)(B), no application under Section 351(k) for which Pneumococcal 15-valent Conjugate Vaccine [Diphtheria CRM₁₉₇ Protein] as the reference product can be submitted until 4 years after the date of licensure of the Pneumococcal 15-valent Conjugate Vaccine [Diphtheria CRM₁₉₇ Protein].

CBER's reference product determination board met on 24 May 2021 and concurred with our recommendation to grant exclusivity. Upon approval, the product will be designated as a reference product and the associated exclusivity periods will be based upon the date of first approval

1.12.14 Environmental Analysis

(By JC) Merck & Co., Inc. has requested a categorical exclusion from the requirements to prepare an Environmental Assessment under 21 CFR §25.31(c). The BLA for Pneumococcal 15-valent Conjugate Vaccine [CRM₁₉₇ Protein], (b) (4) meets the requirements of a categorical exclusion under this CFR section because the intended new vaccine consists of materials that occur naturally in the environment and manufacture or use of the vaccine will not alter significantly the concentration or distribution of the substance, its metabolites or degradation products in the environment.

Reviewer Assessment: (JC) The categorical exclusion is justified.

Module 3

3.2.S DRUG SUBSTANCE

3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties


(By JC) Pneumococcal 15-valent Conjugate Vaccine [CRM₁₉₇ Protein], (b) (4) (VAXNEUVANCE) drug substance (DS) components are composed of pneumococcal polysaccharide (PnPs) serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F individually conjugated to the CRM₁₉₇ carrier protein. Each purified conjugate bulk is a distinct drug substance referred to as the serotype-specific monovalent bulk conjugate (MBC). Thirteen of the MBC (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F) are very similar to those currently available in the Prevnar 13™ vaccine manufactured by Wyeth, a subsidiary of Pfizer (see polysaccharide structures to follow).

Added serotypes are 22F, and 33F. (b) (4)

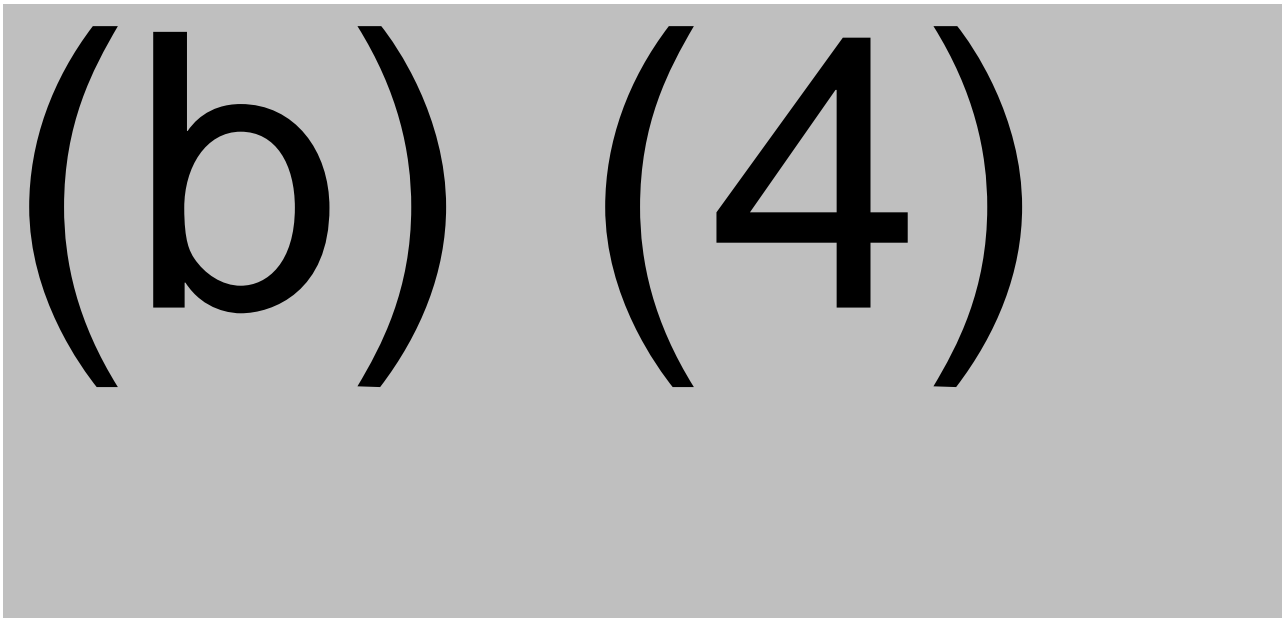


80 pages determined to be not releasable: (b)(4)


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3.2.S.4 Control of Drug Substance

3.2.S.4.1 Specification(s) and 3.2.S.4.5 Justification of Specification(s)

(b) (4)

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3.2.P DRUG PRODUCT

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

(JC) V114 Drug Product (DP) is a sterile opalescent liquid suspension for injection. The DP provides a total of (b) (4) of total Pneumococcal Polysaccharide (PnPs) Antigens conjugated to CRM₁₉₇ (b) (4) 30 µg/mL) as Monovalent Bulk Conjugate (MBC) (b) (4)

The targeted composition for the V114 formulation per 0.5 mL dose is presented in Table 1 of Section 3.2.P.1 DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT and repeated below in Table 7.

The DP is filled into a 1.5 mL glass syringe and stored at 2–8 °C. The combination product consists of V114 DP aseptically filled into the syringe barrel assembly and closed with a plunger stopper. Final device assembly includes the addition of the plunger rod to the filled and stoppered syringe container. The V114 combination product is defined as the syringe with plastic rigid tip cap, filled and stoppered, and with plunger rod inserted, as shown in Figure 1 of Section 3.2.P.1.

Reviewer Comments: (JC/EK)

The description of the composition of the DP is adequate. However, it is not clear why the amount of CRM₁₉₇ is only 30 µg/mL (b) (4). Examination of the MBCs in batch release and stability studies indicates that the Saccharide to Protein ratio is close to (b) (4) basis, so a more realistic amount would be closer to (b) (4) 30 µg/dose. We assume that the estimate is based on the lower end of the limits of the Saccharide/Protein ratio for each MBC, but this is not realistic based on the information supplied. An IR was transmitted on 23 April 2021 to address the actual amount of CRM₁₉₇ in the DP. A response was received 30 April 2021. Table 1 of Section 3.2.P.1 DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT was corrected to reflect (b) (4) 30 µg/dose. The response is acceptable.

Table 7. V114 Composition

Description	Input Material	Requirement		Function	Quality Standard
		(b) (4)	Dose (0.5 mL)		
Active Ingredients (MBC)	1	(b) (4)	2 µg	Active	Internal Specification
	3				
	4				
	5				
	6A				
	6B	(b) (4)	4 µg		
	7F	(b) (4)	2 µg		
	9V				
	14				
	18C				
	19A				
	19F				
	22F				
	23F				
	33F				
Protein	CRM ₁₉₇	(b) (4) 30 µg/mL	(b) (4)		
Inactive Ingredients	Aluminum Phosphate (Al ³⁺)	(b) (4)	125 µg	Adjuvant	Internal specification
	Polysorbate – 20	(b) (4)	1 mg	(b) (4)	(b) (4)
	L-Histidine	(b) (4)		Buffer	(b) (4)
	Sodium Chloride	(b) (4)		(b) (4)	(b) (4)
	Water for Injection	(b) (4)		(b) (4)	(b) (4)

(b) (4)

3.2.P.2 Pharmaceutical Development (JC)

3.2.P.2.1 Components of the Drug Product

V114 DP is formulated and filled into syringes at the (b) (4) facility. The prefilled syringe is considered a combination product after the plunger rod is inserted at the packaging facility in the (b) (4) facility.

3.2.P.2.1.1 Drug Substance

(b) (4)

3.2.P.2.1.2 Excipients

A list of the DP components including the excipients and their functions in the final DP is provided in Table 6 of this review. The choice of excipients and their influence on DP performance is described along with assessment of the compatibility of V114 MBC's with other components in the DP and with excipients is demonstrated by formulation studies in Section 3.2.P.2.2 Drug Product Formulation Development.

Aluminum phosphate adjuvant enhances the immunogenicity of V114. The applicant reports that the aluminum-based adjuvant induced higher anti-PnPs responses than V114 vaccine formulations that did not include any adjuvant.

L-histidine serves as a buffer to maintain the formulation's (b) (4) in a (b) (4) during manufacture and storage. This buffer is considered appropriate with a buffering range of (b) (4) with a (b) (4) of (b) (4)

Sodium chloride serves to produce an isotonic environment (b) (4) for the injection which results in a less painful injection.

Polysorbate – 20 serves as a (b) (4) to prevent aggregation of the DP components during manufacture and storage especially under (b) (4) conditions. Titration studies identified a minimal concentration of (b) (4) to serve this purpose, which is the concentration used in the final formulation.

Finally, water for Injection (WFI) is used to prepare the buffers to dilute the active and inactive ingredients to the appropriate concentration.

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

A process Hazard Analysis approach was undertaken to assess potential hazards, hazardous situations and events that may cause potential harm to product quality, rank the potential risk according to severity of the harm. The approach also determined the probability of a hazard to result in the harm and the ability to detect the hazard, hazardous situation, or harm. Risk scoring was completed in line with ICH Q9 guideline. The approach was utilized to classify parameters and their potential impact on CQA. Those determined to have greater than a negligible impact were determined to be CPPs.

A range of Lab-Scale developmental studies were conducted to investigate: (b) (4)

[REDACTED]

Laboratory scale Stability and Comparability Studies were conducted. These included: (b) (4)

[REDACTED]

Process development at the (b) (4) manufacturing site performed the following activities in the formulation development process: (b) (4)

[REDACTED]

Syringe filling was developed through studies focused on: (b) (4)

[REDACTED]

The V114 DP formulation has been evaluated with or without the presence of an Aluminum Phosphate Adjuvant (APA) and with or without a surfactant (b) (4) Polysorbate-20 (PS-20) (b) (4). The formulation development process was introduced into clinical trials. The trial phase and lots included (in parentheses) indicated as follows: Phase 1 (V114-001), Phase 2/2A (V114-001 – 004), Phase 2 (V114 005 – 007), Phase 2B (V114 – 008) and Phase 3 and commercial process (V114 016 – 033).

Formulation Development for use in V114-004:

Phase 1 essentially tested the DP formulated with and without aluminum phosphate adjuvant and amount of antigen. Mean titers were reported. It was found that (b) (4) µg/mL was optimal for all except for 6B which was 4 µg /mL. APA range was also tested as well as relative potency

The (b) (4) DP Formulation:

Phase 2/2A was undertaken after modification of some MBC manufacturing processes previously described in Section 3.2.S.2.6. including (b) (4)

(b) (4) These experiments were performed at (b) (4) was shown to (b) (4). PS – 20 was eventually chosen based on overall characteristics.

(b) (4) : DP formulations were prepared at lab-scale to evaluate (b) (4) MBC and (b) (4). A dose ranging study was conducted with concentrations of PnPs ranging from 2 µg/mL (b) (4). Serotype specific antibodies tended to be higher at a dose of (b) (4), all serotypes except 6B (b) (4) serotype 6B.

Formulation Composition and Manufacture of the V114 DP used in V114-004:

The formulation compositions of the V114 DP formulations consisted of (b) (4) L-histidine, (b) (4) NaCl, (b) (4) with (b) (4)

Formulation Development for use in V114-005, V114-006 and V114-007:

Following evaluation of the clinical results for V114-004 additional process changes were made to improve DS attributes to further enhance the efficacy of the vaccine. Modifications were made to the DS conjugation process and DP formulation.

Modifications made to the DS conjugation process (b) (4). Improvements were made (b) (4) and improve on other key quality attributes.

The (b) (4) DP Formulation:

It was determined that (b) (4) was not sufficient to (b) (4)

(b) (4)

Formulation Composition of the V114 DP used in V114-005, -006, and -007:

Following evaluation of the clinical results for V114-004 it was determined that V114 DP required additional process changes to improve DS attributes to further enhance the efficacy of the vaccine. The following changes were made. The manufacturing process for (b) (4)

Development of Optimized DP Manufacturing Process for use in V114-008 Study:

Subsequent to comparison of results associated with V114-(b) (4) V114-(b) (4), V114-(b) (4) and V114-(b) (4), the selected (b) (4) V114 – (b) (4) clinical study and was (b) (4) of total PnPs which included (b) (4) per serotype except for 6B at (b) (4). MBCs (b) (4)

. Excipients were (b) (4) L-histidine, (b) (4) Sodium Chloride, (b) (4) APA, (b) (4) PS-20 at (b) (4)

Optimization of the DP Manufacturing Process:

(b) (4)

Optimization of the DP Manufacturing Process:

DP formulation and filling operation was (b) (4)

Development of (b) (4) commercial-scale process for Phase 3 and Formal Stability Studies (FSS):

After examination of the clinical results from V114 – (b) (4) the scale of the process was (b) (4) To accommodate the (b) (4)

(b) (4) to Support the Final DP Manufacturing Process:

To support the final manufacturing process, the V114 (b) (4) was scaled for both manufacture at (b) (4)

(b) (4) . Acceptable (b) (4) at each (b) (4) was determined for the (b) (4)

Laboratory Development of the Final DP Manufacturing Process for Phase 3:

Initial Phase 3 studies were manufactured at (b) (4) commercial-scale (b) (4). Due to DS limitations, a lab-scale (b) (4) study was initiated to develop the (b) (4) commercial-scale manufacturing process (b) (4) for Phase 3.

Impact of Scale (b) (4) on the DP Formulation:

The impact of manufacturing scale (b) (4) on the DP the batch was placed on stability at (b) (4)

there was little impact to the DP when tested using saccharide content (b) (4)

Comparison of the (b) (4) Commercial-Scale Process to the V114- (b) (4)

Manufacturing Process:

A direct comparison of the (b) (4) as measured by saccharide content (b) (4) was made between the (b) (4) lab-scale batch and the V114- (b) (4) clinical batch (b) (4). No significant differences were revealed between the V114- (b) (4) clinical batch and (b) (4) commercial-scale manufacturing process as assessed by the saccharide (b) (4)

V114 DP Formulation Composition and DP Manufacture – Initial Phase 3 (V114-016, 017, 018, 021, 022, 023, 024, 027, 028, and 031) Studies:

The following DP manufacturing process changes were implemented between Phase 2 and initial Phase 3. Changes included (b) (4) (Phase 2, V114-008) to (b) (4) (Phase 3). (b) (4) method used to measure (b) (4) was an improved version.


Comparability between (b) (4) DP manufacturing was demonstrated to support the number of clinical doses, the Phase 3 Clinical, Lot Consistency and Formal Stability Studies were manufactured at both manufacturing sites.

V114 DP Manufacture – Phase 3 (V114-019, V114-020, V114-022, V114-025, V114-026, V114-027, V114-029, V114-030, V114-032 and V114-033) and FSS:

The process was scaled to (b) (4) and the (b) (4) process is outlined in Figure 17 of 3.2.P.2.2 FORMULATION DEVELOPMENT.

Reviewer Comments: (JC)

(b) (4)



3.2.P.2.2.2 Overages (JC)

No overages are described

3.2.P.2.2.3 Physicochemical and Biological Properties (JC)

The Drug Product is composed of the 15 MBC Drug Substances formulated with sodium chloride, Polysorbate – 20, L-histidine, aluminum phosphate and WFI. There are no

physiochemical 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 (JC)

The manufacturing process is summarized in this memorandum 3.2.P.3.3 Description of Manufacturing Process Table 6. The formulation and filling processes have been maintained, with minor optimizations, throughout the development of V114. Laboratory scale activities were conducted at the (b) (4) manufacturing facility. Minor process differences required for (b) (4) were described in this section. Phase 1 Clinical Supplies; Phase 2 Clinical Supplies; Phase 3 Clinical Supplies and FSS were produced at the (b) (4) facility. Phase 3 Clinical Supplies; FSS, and Commercial Product were produced at the (b) (4) site. DS for the former were supplied by (b) (4) (b) (4). The latter used DS supplied by (b) (4).

The Process Risk Analysis (PHA) methodology was used to identify all potential hazards, hazardous situations and events that may cause potential harm to product quality, rank the potential risk according to severity of the harm, probability of the hazard to result in the harm and the ability to detect the hazard, hazardous situation or harm. Risk scoring was completed in line with ICH Q9 guideline. Parameters of consequence were defined as having potential impact on a CQA if an issue were to occur and of a probability of occurrence greater than negligible. Such parameters were defined as critical process parameters (CPP's). Following completion of the assessment the CPP's identified were implemented in the control strategy and shown in the dossier Section 3.2.P.3.3 Description of Manufacturing Process and Process Controls. The PHA scoring methodology used in the studies can be found in the dossier section in Table 9.

Process development studies performed at laboratory scale performed at the (b) (4) site include the following: (b) (4)

(b) (4) studies. Studies performed at the (b) (4) commercial site included (b) (4)

All studies were adequately monitored with appropriate physical and/or chemical/biochemical monitoring processes. The saccharide (b) (4) assay was used extensively, for instance in (b) (4) studies. All data trends were within predefined ranges, which were appropriate.

Dose (b) (4) studies were performed at commercial scale at the (b) (4) facility. Impact of (b) (4) were evaluated. (b) (4)

. This designation was appropriate.

Risk assessment activities were conducted resulting in process development and optimization of the formulation and fill processes. The studies conducted generated a knowledge base which allowed for remediation of gaps in the process and evolution in the process throughout development. The information in this section support the conclusion that an appropriate formulation and fill process is in place. The activities serve as a support of DP validation studies at (b) (4). The manufacturing process based on this design space is defined in Section 3.2.P.3.3 Description of Manufacturing Process and Process Controls, with process control strategy is described in Section 3.2.P.3.4 Control of Critical Steps and Intermediates. Results from the PPQ campaign are found in Section 3.2.P.3.5 Process Validation and/or Evaluation. Activities in support of the DP manufacturing process were appropriate.

3.2.P.2.4 Container Closure System (JC)

The prefilled syringe components include the syringe barrel, plastic rigid tip cap, and plunger stopper. Syringe barrels are assembled with tip caps and sterilized by the vendor using (b) (4) prior to delivery as ready-to-use. Stoppers are sterilized by (b) (4) and are ready to use. The polypropylene plunger rod does not have direct contact with the DP suspension and therefore is not considered a primary packaging component. The suitability of the container system has been investigated based upon: (b) (4) testing and ISO standards for prefilled syringe components, extractable and leachables assessments, long term stability, container closure integrity and photostability according to ICH Q1B guidelines.

Suitability of the container system:

The chemical/physical characterization and the materials of construction, along with a review of the biological safety testing, were reviewed. The ISO (b) (4) biological safety endpoints for the prefilled syringe have been fulfilled. The assessment is presented in the file and entitled BIOLOGICAL RISK ASSESSMENT REPORT BRAR001.

Extractables studies:

A controlled extraction study of the syringe components that contact the V114 formulation (glass syringe, plastic rigid tip cap and plunger stopper) was performed to validate methods to monitor leachables in the V114 formulation throughout the intended shelf life.

(b) (4)

The conditions of extraction and analysis were described in the study report entitled CEL-RPT-000251: Extractables and Leachable Evaluation for the Syringe and Vial Components used in V114 Drug Product. (b) (4)

(b) (4)

. According to ICH guidelines for Class (b) (4) under ICH Q3C(R5) extractable values do not exceed these limits, the use of this syringe, vial, stopper, plunger stopper and tip cap does not present a significant risk to patient safety, and the components are, therefore, suitable for use.

Leachables studies:

(b) (4) methods were developed and validated to monitor leachables in V114 drug product throughout the intended shelf life. These included (b) (4)

Specifics of the methods used and resulting data can be found in the report (CEL-RPT-000251). (b) (4)

(b) (4) [REDACTED] were observed. (b) (4) [REDACTED]

[REDACTED]. Overall, based on leachables detected, likely there is little significant impact on drug product safety.

Reviewer Comments: (JC)

Based on (b) (4) testing, ISO standards for prefilled syringe components, extractable and leachables assessments, long term stability, container closure integrity and (b) (4) related information, the container system is suitable for the V114 vaccine product.

3.2.P.2.5 Microbiological Attributes

(JC) The DS is formulated as a (b) (4)

A (b) (4) examination of the drug product formulation is performed on the filled DP using (b) (4) methods as described in Section 3.2.P.5.3 Process Validation and/or Evaluation – (b) (4). Verification testing for endotoxin is also performed as described in dossier Section 3.2.P.5.3 Process Validation and/or Evaluation – (b) (4). Additionally, container closure integrity (CCI) validation, release and stability testing has been performed. Shipping qualification has also been performed as described in dossier Section 3.2.P.3.5 Process Validation and/or Evaluation – Shipping Qualification. CCI results from combination product samples were compared to CCI results from the associated prefilled syringe lots and the results were comparable.

Reviewer's Assessment: (JC)

There were no microbiological attribute deficiencies identified.

3.2.P.2.6 Compatibility (JC)

The applicant performed leachable and extractable studies on the syringe container using appropriate (b) (4) and representatives of DP to determine any such leachable or extractable compounds or metals and compared to safety limits as described above.

(b) (4) studies were also performed. There were no issues identified concerning compatibility of the DP and container.

Reviewer's Assessment: (JC)

There were no compatibility issues identified.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

(JC)

Sites of activities for manufacturing, assembly and testing activities are shown below:

1. Merck Sharpe & Dohme (b) (4) –
 - a. DP formulation, fill and inspection
 - b. Aluminum Phosphate Adjuvant (APA) Manufacture testing and release (microbiological)
 - c. DP release and stability testing (microbiological)
 - d. DP release
2. (b) (4) –
 - a. APA testing and release (chemical)
 - b. DP release and stability testing (chemical)
3. (b) (4)
 - a. DP release and stability testing
 - b. Secondary packaging (syringe, pre-filled syringe device assembly and labelling)
 - c. Finished goods release
4. (b) (4)
 - a. DP stability testing (Contain closure integrity)
5. (b) (4)
 - a. DP stability testing (Combination product)

3.2.P.3.2 Batch Formula

(JC)

The batch formula is given for a typical (b) (4) batch rather than a generalized formula. Inspection of the listed ingredients, their amounts, and review of and checking of calculations verifies that the sample formulation given is correct according to expected formulation presented in the composition description.

Reviewer Assessment: (JC)



The batch formula is adequately described.

3.2.P.3.3 Description of Manufacturing Process

(b) (4)



(b) (4)

Reviewer Comment: (JC)

The in-process tests and CPP are appropriate and sufficient. There are no apparent deficiencies in the formulation and fill process according to the information presented.

3.2.P.3.4 Controls of Critical Steps and Intermediates

(JC)

The formulation process is controlled with the use of a series of chemical and serological tests as shown in Figure 2 of Section 3.2.P.3.3. Acceptance criteria have been established and appear appropriate. (b) (4) are tested where appropriate. MBC (b) (4) is also tested. (b) (4), The fill CPP is (b) (4), is classified as a CPP Acceptance criterion, has been assigned, and centers on (b) (4) which is the (b) (4) associated with standard dose.

Reviewer Assessment: (JC)

The in-process tests and CPP are appropriate and sufficient. There are no apparent deficiencies in the formulation and fill process according to the information presented

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

3.2.P.4 Control of Excipients

(JC)

3.2.P.4.1 Specifications

There are no excipients used in the manufacture of V114 Drug Product of human or animal origin. There are no novel excipients used in the manufacture of V114 Drug Product. Compendial excipients include sodium chloride, Polysorbate – 20, L-histidine, and WFI. All are maintained according to (b) (4) reference quality standard. Polysorbate – 20, L-histidine, (b) (4) and WFI are maintained according to (b) (4) reference quality standard.

3.2.P.4.2 and 3.2.P.4.3 Production Process for Aluminum Phosphate Adjuvant, Analytical Procedures and Validation of Analytical Procedures

(JC)

Buffers and salt solutions:

All excipients, including histidine, sodium chloride, and phosphate, are tested to comply with the reference quality standard, (b) (4) as applicable.

Aluminum Phosphate Adjuvant (APA):

Manufacture of APA was referenced in this section and described in Section 3.2.A.3. It is reviewed herein. (b) (4)

Release and Stability acceptance criteria are included.

(b) (4)

acceptance criteria were met.

. All

(b) (4)

Reviewer Comments (JC)

The production process for APA is acceptable. The process and analytical procedures used in the process can be considered validated. All validations including that for excipients and APA are appropriate and acceptable. Stability studies support an expiry of (b) (4) as requested.

3.2.P.4.4 Justification of Specifications (JC)

All specifications used in testing of excipients are compliant with (b) (4) as specified. Those for APA are justified.

3.2.P.4.5 Excipients of Human or Animal Origin (JC)

There are no excipients of human or animal origin used in the production of V114 DP.

3.2.P.4.6 Novel Excipient (JC)

There are no novel excipients used in the production of V114 DP.

Reviewer Assessment (JC)

The information provided is acceptable. No deficiencies were identified.

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) (JC)

The release and stability acceptance criteria for the DP have been established in consideration of ICH Q6B, (b) (4)

Clinical Phase 3, and GMP batches manufactured at commercial scale were the primary datasets used in the formal statistical analysis. The tests and justifications are reviewed below. The tests and available specifications are listed in Table 11 in this memo.

Appearance-Opalescence

This is a (b) (4) test and was shown to adhere to the (b) (4) method.

Identity by (b) (4)

This test was developed and aligned with the assay test Saccharide Content (b) (4).

Saccharide Content (b) (4)

The assay is based on the (b) (4)

(b) (4). One of those studies V114 – 004, supported safety and immunogenicity across the range but reported as immunogenicity levels proved to be highest in the current formulated dose. While the clinical data may provide limited support for a range of antigen content, the stability data do not support such wide ranges for Stability specifications.

Conjugated Saccharide Content by (b) (4)

The assay is based on the (b) (4)

(b) (4)

Polysorbate-20

The PS-20 is analyzed using (b) (4)

The formal statistical analysis with currently available release data confirms

with a $\geq 95\%$ confidence that the DP will be within the (b) (4) release specification. Release specification is (b) (4)

(b) (4)

Aluminum

The measured aluminum content of the APA confirms a target of (b) (4). The range was established as (b) (4) which is approximately (b) (4). The formal statistical analysis using currently available release data confirms with a $\geq 95\%$ confidence that the DP will be within (b) (4).

Sterility

The method for sterility is performed in alignment with (b) (4). The commercial specification for Sterility is “No Growth” at release for both (b) (4) Final Container.

Endotoxin

The Endotoxin method for drug product is performed in alignment with (b) (4). The acceptance criterion for release of DP has been (b) (4).

(b) (4)

Container Closure Integrity Testing

Due to the presence of the vaccine adjuvant in DP, (b) (4) was selected as the CCI method in favor of alternate methods such as (b) (4). (b) (4) has been used to support DP Clinical, FSS, and PPQ testing. A review of available stability data confirms the ability to routinely meet the established CCI limit of “No leaks detected”.

(b) (4)

Chloride Content

The formal statistical analysis with currently available release data confirms with a $\geq 95\%$ confidence that the DP will be within current (b) (4) release criteria.

Histidine Content

The formal statistical analysis with currently available release data confirms with a $\geq 95\%$ confidence that the DP will be within the current (b) (4) release criteria.

Information Requests

IRs were transmitted on 5 March 2021 and 26 March 2021 concerning the submitted specification ranges for the Saccharide Content and Conjugated Saccharide (b) (4) assays. Responses were received on 12 March 2021 (125741/0.020) and April 2, 2021 (125741 0.025).

Your specification ranges for the Saccharide Content drug product release test appear broad at (b) (4) of target based on the batch release data presented in the filing. Similarly, the specification ranges for drug product stability for both Saccharide Content and Conjugated Saccharide Content tests are also broad based on the submitted information. Additionally, we note that you have not included the Conjugated Saccharide Content assay (b) (4) Saccharide as release tests. Please address the following:

a) Please include the Conjugated Saccharide Content (b) (4) Saccharide Tests in your Release Tests Panel.

b) Please provide updated Stability Specification ranges for the Saccharide Content and Conjugated Saccharide Assays based upon a statistical analysis of your current data and stability projection estimates. We recommend that you reevaluate your Saccharide Content and Conjugated Saccharide Content tests specifications after accumulation of a (b) (4) batches to evaluate the process capability and estimate specification limits. Please acknowledge.

Merck did agree to tightening of specifications for the Saccharide Content and Conjugated Saccharide Content (b) (4), and provided a commitment shown below. The company did not agree to include the Conjugated Saccharide Content (b) (4) Saccharide Tests in the Release Tests Panel in the 12 March 2021 response. Essentially, concerning inclusion of (b) (4) Saccharide and Conjugate Saccharide (b) (4) in the Release Panel, the company argues that these qualities are tracked in (b) (4) release panel and, therefore tracking these qualities in the DP are not required. The follow-up IR transmitted to Merck on 26 March 2021 appears below. The company did finally agree to include Conjugated Saccharide Content (b) (4) Saccharide Tests in the Release Tests Panel.

We do not concur with your proposal to not include the Conjugated Saccharide (b) (4) assay and Total Saccharide Content in your Drug Product (DP) release protocol. The (b) (4) shelf-life ranges from (b) (4) depending on the serotype as described in Section 3.2.S.7.1, Stability Summary and Conclusions (b) (4) page 11. The (b) (4) for formulation of DP which has a proposed shelf-life of 18 months. Your (b) (4) stability program does not account for the differences in matrix or related chemical environment properties imparted by the formulation process, nor the added time incurred at the formulated DP level. Further, your proposal to not include the Conjugated and Total Saccharide Content (b) (4) assays in the DP release specifications do not allow formal monitoring of these attributes as controls in the formulation and fill aspects of your manufacturing process.

Inclusion of the Total Saccharide and Conjugated Saccharide Content (b) (4) assays provides controls of the formulation and fill process and unforeseen issues affecting related attributes including the conjugates (b) (4) saccharides. Moreover, your stability protocol requires (b) (4) assays. Therefore, as these (b) (4)

We consider that formulation may occur at various (b) (4)

We agree that theoretical Conjugated Saccharide Content based on the (b) (4) performed at the DP level with Conjugated Saccharide and Saccharide Content (b) (4) assays in your cited batches. However, these arguments do not control for issues related to DP formulation, fill or issues that may occur (b) (4). Thus, we recommend that your Conjugated Saccharide and Saccharide Content (b) (4) assays serve as control for Total Saccharide, (b) (4) saccharide and conjugate amounts (b) (4) and any unforeseen issues that may occur. Therefore, the measurement of (b) (4) saccharide and conjugates at the DP level are not redundant as you state on page 19 of your IR response. Please include the Conjugated Saccharide Content (b) (4) Saccharide Tests in your Drug Product Release Tests Panel. Please acknowledge.

Commitment:

The Applicant acknowledges and commits to reevaluate Saccharide Content and Conjugated Saccharide Content specifications after collection of sufficient batch and

real time stability data to evaluate the process capability and estimate specification limits (e.g. minimum of 20 commercial batches).

Merck also agreed to include the Conjugated Saccharide Assay (b) (4) Saccharide in the release panel. Merck states in the April 2, 2021 response:

Section 3.2.P.5.1 Specifications have been updated to include the Conjugated Saccharide (b) (4) as both release and stability requirements.

Reviewer Assessment (JC)

With the exception of the Saccharide and Conjugated Saccharide (b) (4) assays, justifications provided for all assays are appropriate. Given the low amount of data available for these (b) (4) assays, and the associated information submitted to justify current specifications, the justifications for the (b) (4) assays are acceptable given the commitments by the company to reevaluate these release and stability specifications. Noted here is that DP release and stability tests: (b) (4) are in process of development as per agreement at the IND stage of the file (14977 6 June 2020). An IR was transmitted (14 April 2021) for an update on the development of these tests and a timeline for implementation. A response from Merck was received 23 April 2021. The IR appears below.

Comment (14 Apr 2021):

In your June 5, 2020 response submitted to IND 14977 to CBER Information Request dated 15 May 2020, you agreed to develop an assay to measure total protein for your DP and evaluate sample preparation techniques to differentiate adjuvant (b) (4) proteins for your stability protocol. You state that the method qualification activities will continue through 2020 and that the details of the status of qualification activities will be communicated to CBER during the BLA review period if requested. You describe that the assay will first be introduced as a characterization tool anticipated to be as late 2020 or early 2021 for use in Formal Stability Studies (FSS) and Process Performance Qualification (PPQ) batches. Please provide an update on the qualification activities for these assays (total protein and (b) (4) to include but not limited to qualification/validation status, FSS and PPQ data for this assay, and an update on expected dates for implementation of the assay as a characterization test, and implementation of the test as a release and stability test.

Response (23 Apr 2021):

The company updated CBER stating that the (b) (4) and total protein methods have been implemented into the FSS and PPQ stability studies as of March 2021 as agreed in the 01477, SN 0189, 02 September 2020 commitments. As per the

previous commitment to the agency, when the stability studies currently in progress are complete (FSS (b) (4) time point in Mar 2022 and PPQ (b) (4) time point in Nov 2022), the data will be assessed for the completed FSS and PPQ batches as well as any in-progress stability batches. These data will be used to determine an appropriate specification.

Reviewer Assessment (JC)

The commitment to continue the FSS and PPQ batches stability studies and timeline remains in alignment with the 02 September 2020 commitment and is appropriate. Release and Stability Specifications are shown in Table 8.

Table 8. V114 Drug Product Final Fill Specifications

Attribute	Test Method	Acceptability	
		Release	Stability
Appearance (Opalescence)	(b) (4)	Opalescent (b) (4)	
Identity (b) (4)	(b) (4)	Presence of Type-Specific Polysaccharides Confirmed	NA
Saccharide Content by (b) (4)	(b) (4)	Serotype 6B: (b) (4) Other Serotypes: (b) (4)	Serotype 6B (b) (4) All other Serotypes (b) (4)
Conjugated Saccharide Content by (b) (4)	(b) (4)	Serotype Criteria 3: (b) (4) 1, 4, 5, 9V, 19A: (b) (4) 6A, 7F, 14, 18C, 19F, 22F, 23F, 33F (b) (4) 6B: (b) (4)	
Aluminum Content (mg/mL)	(b) (4)	(b) (4)	NA
Polysorbate-20 (b) (4)	(b) (4)	(b) (4)	NA
(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	
(b) (4)	(b) (4)	(b) (4)	
(b) (4)	(b) (4)	NA	(b) (4)
Container Closure Integrity	(b) (4)	NA	No Leaks detected ^a
Endotoxin (EU/mL)	(b) (4)	(b) (4)	NA
Sterility	(b) (4)	No growth	

^a Result will be reported as conforms for a passing result

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

(JC)

Appearance

(b) (4) Drug Product (DP) samples were tested as part of this verification meeting all pre-determined acceptance criteria.

Conjugated Saccharide (b) (4)

The assay method was validated in accordance with ICH Q2(R1), the validation focused (b) (4)

All predetermined acceptance criteria were met.

(b) (4)

Sterility

The test results have demonstrated that the (b) (4) test for sterility is suitable under the test conditions at (b) (4) for the V114 DP syringes and the (b) (4)

Endotoxin

Based on the results of the verification studies, the (b) (4) used for determination of endotoxin are considered validated and suitable for use for V114 DP syringe at the (b) (4) testing site.


Aluminum Content

The assay method was validated in accordance with ICH Q2(R1); the validation focused on accuracy, linearity, range, precision, and specificity with predefined acceptance criteria. Robustness was also tested. Method validation was conducted at (b) (4). All predetermined acceptance criteria were met. The (b) (4) assay is validated at the (b) (4) testing site for the determination of aluminum content in V114 DP.

Polysorbate – 20 Content

The (b) (4) method was validated in accordance with (b) (4)

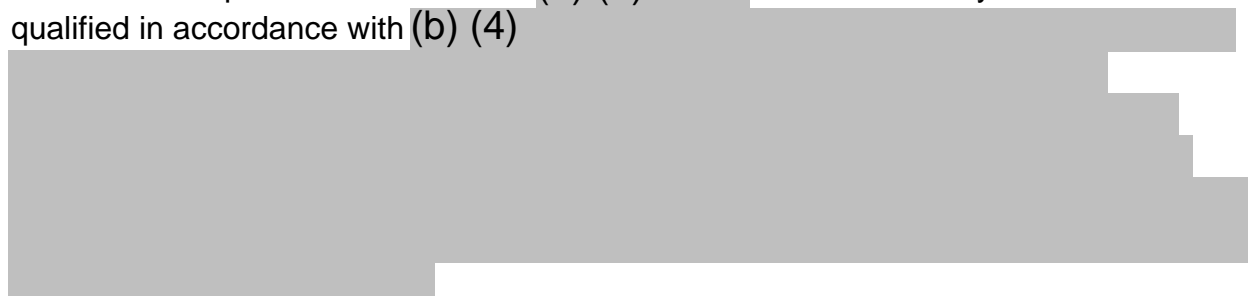
(b) (4)

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The IR was transmitted 1 February 2021. The response was received 10 February 2021. A second IR was sent in response and the response received on 25 February 2021. DBSQC has requested revalidation of the assay and Merck has agreed. See DBSQC Review of this assay for further details.

Identity and Saccharide Content Assay (b) (4)

Activities were performed at both the (b) (4) sites. The assay method was qualified in accordance with (b) (4)

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(b) (4)

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(b) (4)

Information Request

An IR was sent on 19 March 2021 to inquire about Acceptance Criteria used in the two validation activities used for the quantitative portion of the test. The IR focused on the (b) (4) in the Specificity parameter and the (b) (4) calculations use in the Linearity and Relative Accuracy parameter of the test. Based on the submitted materials different calculations were used when analyzing these two parameters. The IR is shown below.

Regarding your Total Polysaccharide (b) (4) assay used in release and stability programs of the drug product, the acceptance criteria and calculations performed in validation reports dated August 2017 (Document # 56085-2016-TR-0071PD) and August 2018 (Document # 56085-2017-TR-0028 REV 01) are different. In 56085-2017-TR-0028 REV 01 you describe (b) (4) validation for Serotypes 3, 4, 5, 9V, 19A, 19F, 22F, 23F, and 33F. All serotypes were not evaluated using the same criteria and procedures. For instance, calculation of (b) (4), and your (b) (4)

. Please submit data so that ultimately all fifteen serotypes are evaluated using the same protocol, similar to what was used during the (b) (4)-validation reported in Document # 56085-2017-TR-0028 REV 01.

A response was submitted in Amendment 1257410.024 dated 26 March 2021. Merck stated that the only difference was in the calculation of (b) (4). The original criterion required “(b) (4)

(b) (4) was considered statistically significant. Using the revised criteria all serotypes tested met the criteria. Data from the remaining serotypes not tested in the supplemental validation were subject to recalculation and all met the new criteria. While it is irregular to apply new Acceptance Criteria in this fashion the difference in (b) (4) is nominal and acceptable.

The calculation of (b) (4) was stated to be the same. Stated in a note in Table 2 of the Information Amendment: “Note the formula in the original validation report has ‘Potency’ not (b) (4)”. The statistical analysis of both studies leveraged the same calculation and formula. Given the totality of the information submitted, only Serotype (b) (4) falls outside of Acceptance Criteria and only for Linearity/Relative Accuracy at the penultimate data point in the linear range. The ultimate datapoint met with acceptance criteria. Given the (b) (4) for the linear range there are no practical concerns for application of the method. The method can be considered validated.

Container Closure Integrity

During validation (b) (4)

(b) (4) to demonstrate the ability of the test method and the instrument to accurately differentiate integral packages from those with defects. specificity, precision, limit of detection, range, accuracy, and robustness were tested. All acceptance criteria were met.

(b) (4)

Reviewers Assessment (JC)

Analytical procedures and test validations were reviewed and were found to be acceptable. The listed tests can be considered validated.

3.2.P.5.4 Batch Analyses (JC)

Batch analyses for V114 (b) (4) and final container vaccine batches used in clinical studies, stability studies, and Process Performance Qualification (PPQ) were presented. Batch analyses were performed throughout vaccine development and coordinated with clinical trial activities. Sites of manufacture included (b) (4) manufacturing facilities. The former was involved in the early (b) (4) and was transferred to manufacturing (b) (4). Phase 3 and Process Performance Qualification lots were manufactured at (b) (4). The Conjugated Saccharide (b) (4) assay was developed late in the IND cycle and was not performed on any presented batch.

Reviewer Assessment (JC)

There are no concerning trends observed. The batch release information presented are acceptable.

3.2.P.5.5 Characterization of Impurities (JC)

No additional impurities are introduced into the V114 Drug Product (DP) during the DP manufacturing process. Any impurities would likely result from degradation processes of the conjugate and these are monitored via protein, saccharide, and conjugate-based assays.

3.2.P.6 Reference Standards or Materials (JC)

DP reference standards include Primary Reference Standards (PRS) and Secondary Reference Standards (SRS). The Primary Reference Standards are sourced from

(b) (4)

. The SRS is (b) (4)

The SRS is (b) (4)

Nevertheless, the SRS is (b) (4)

The current reference standards are linked to clinical trials Phase 3 clinical supplies for both Protocol 019 and Protocol 020 as described in Sections 3.2.P.2.3.

(b) (4)

Reviewer Comment (JC)

The reference standards, performance monitoring program, stability program, link to clinical data, characterization and contingency plan for replacement are appropriate. The reference standards and associated program are acceptable.

3.2.P.7 Container Closure System (JC)

The extractables and leachables studies for the syringe were covered in section 3.2.P.2.4 Container Closure System of this memo. The following are provided lot to lot from (b) (4), the vendor of the device. The (b) (4) syringe is certified as (b) (4)

The syringe barrel conforms to specifications and schematics. The plastic component has been qualified in accordance with biological testing ISO (b) (4) current edition: Biological evaluation of medical device. The plunger rods meet material conformity based on Biological testing of the ISO (b) (4) standards. The rods also conform to specifications and schematics drawings

Reviewer Assessment (JC)

The information provided is acceptable.

3.2.P.8 Stability (JC)

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

One Clinical Phase 3 batch (b) (4) and (b) (4) DP batches (FSS and PPQ) are enrolled in primary stability study in the prefilled syringe container closure system. (b) (4) DP batches manufactured at the final commercial formulation and fill site (b) (4) were included. These were held at the recommended (2 - 8 °C, (b) (4) storage temperature, 5 °C . Up to 18 months of commercial scale lot data were available. (b) (4) of data are available for (b) (4) lot. The proposed shelf-life is 18 months.

Supportive testing was also performed at alternative conditions including at (b) (4)

(b) (4)

(b) (4)

Reviewer Assessment (JC)

The information presented support the requested 18 months expiration. It should be noted that Serotypes 6B, 19A and 19F all show some evidence of degradation based on (b) (4) test results. While these serotypes remain within specifications at 18 months, (b) (4).

3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment (JC)

Merck's stability commitments establish the following tests for inclusion in the stability program: Appearance – Opalescence, Saccharide Content by (b) (4), Conjugated Saccharide Content by (b) (4), Container Closure Integrity, Sterility, (b) (4)

The company also includes that following tests listed as Characterization tests: (b) (4)

Validation data for the (b) (4) assays were presented in this section. These tests were developed late in the IND cycle. The validations are acceptable. Specifications for the Stability Protocol are listed for any test in this section. They are available in Section 3.2.P.5.1 SPECIFICATIONS and do not include (b) (4). There is no plan in place to govern updating of specifications as more data becomes available. There are no information describing the implementation schedule and method to be used to ascribe specifications for (b) (4)

Reviewer Assessment (JC)

While in general the Stability Protocol proposed is acceptable there are some deficiencies. There are no specifications described for (b) (4) assays. These assays were in developed late in the IND cycle. An update was requested in an Information Request on 15 April 2021. The company's response was received 23 April 2021. The IR is shown below. In the 5 June 2020 communication during the IND stage of the review process Merck agreed to develop assays to measure (b) (4). Both assays would be developed and

qualified for implementation as characterization tools no later than early 2021 and complete testing after implementation on FSS and PPQ batches in 2022.

IR COMMENT 1 (15 Apr 2021). In your response (14977.175) to the Agency communication to IND 14977 dated 15 May 2020, you agreed to develop an assay to measure total protein for your drug product and evaluate sample preparation techniques to differentiate adjuvant (b) (4) proteins for your stability protocol. You state that the method qualification activities will continue through 2020 and that the details of the status of qualification activities will be communicated to CBER during the BLA review period if requested. You describe that the assay will first be introduced as a characterization tool anticipated to be as late 2020 or early 2021 for use in FSS and PPQ batches. Please provide an update on the qualification activities for these assays (total protein and (b) (4)) to include but not limited to qualification/validation status, FSS and PPQ data for this assay, and an update on expectation dates for implementation of the assay as a characterization test, and implementation of the test as a release and stability test.

Merck's Response (23 Apr 2021)

The (b) (4) and total protein methods qualification studies have been complete. The method has been added to ongoing FSS and PPQ stability studies as a characterization attribute. It was introduced in March 2021. When the FSS and PPQ (b) (4) month time points (Nov 2022) are complete the data will be assessed along with any transitional in-process stability batches. These data will be used to determine appropriate specifications for the test.

Reviewer Assessment (JC)

The company's response is in line with the agreement set in interactions during the IND review. The response is acceptable.

The Stability specification range assigned for Saccharide Content and Conjugated Saccharide Content assays are very broad compared to available data of Batch release data as well as lots held on stability. These should be re-evaluated and after accumulation of an agreed upon number of commercial batches, re-evaluated provide estimated updated and improved ranges to monitor product and further narrow ranges within the product is actually formulated. All quantitative tests should be evaluated in this way after an agreed upon accumulation of commercial scale lots using a defined procedure with established confidence intervals. An IR has been constructed to address these issues for Saccharide Content and Conjugated Saccharide Content assays.

An IR was sent on 5 March 2021. Merck's response was received on 12 March 2021. A second IR was sent 26 March 2021. The interaction is detailed below:

IR COMMENT 7 (5 March 2021): Your specification ranges for the Saccharide Content drug product release test appear broad at (b) (4) of target based on the batch release data presented in the filing. Similarly, the specification ranges for drug product stability for both Saccharide Content and Conjugated Saccharide Content tests are also broad based on the submitted information. Additionally, we note that you have not included the Conjugated Saccharide Content assay (b) (4) Saccharide as release tests. Please address the following:

IR COMMENT: Please include the Conjugated Saccharide Content (b) (4) Saccharide Tests in your Release Tests Panel.

Merck's Response (12 March 2021):

1. Both (b) (4) content are monitored at the DS level for each of the monovalent bulk conjugates (MBC), and have demonstrated highly stable profiles over their full shelf-life.
2. The Drug Product (DP) process, whereby the 15 individual MBCs are (b) (4)
3. Available DP Conjugated Saccharide Content (b) (4) data confirm for each serotype that the polysaccharide is predominantly conjugated to the carrier protein: the (b) (4) stability results from the Conjugated Saccharide (b) (4) are in close agreement with the Saccharide Content results and can be found in Section 3.2.P.8.3 Stability Data FSS and PPQ.

CBER Response (26 March 2021): We do not concur with your proposal to not include the Conjugated Saccharide (b) (4) assay and Total Saccharide Content in your Drug Product (DP) release protocol. The MBC DS shelf-life ranges from (b) (4) depending on the serotype as described in Section 3.2.S.7.1 page 11. The MBC can be (b) (4) of DP which has a proposed shelf-life of 18 months. Your DS stability program does not account for the (b) (4) DP level. Further, your proposal to not include the Conjugated and Total Saccharide Content (b) (4)

assays in the DP release specifications does not allow formal monitoring of these attributes as controls in the formulation and fill aspects of your manufacturing process.

Inclusion of the Total Saccharide and Conjugated Saccharide Content (b) (4) assays provides controls of the formulation and fill process and unforeseen issues affecting related attributes including the conjugates (b) (4) saccharides. Moreover, your stability protocol requires (b) (4) assays. Therefore, as these (b) (4) are taken at release, they would already exist and add little if any burden to inclusion in the release panel. We consider that formulation may occur at various time-points from beginning to end within the shelf-life of each MBC. Degradation in any specific MBC lots may be undetected since all lots are not monitored on stability. The (b) (4) assays control for these and possibly other issues that can arise during MBC storage, formulation, and fill.

We agree that theoretical Conjugated Saccharide Content based on (b) (4) polysaccharide measurements for the (b) (4) batches may support measurements performed at the DP level with Conjugated Saccharide and Saccharide Content (b) (4) assays in your cited batches. However, these arguments do not control for issues related to DP formulation, fill or issues that may occur during storage of unmonitored MBC lots. Thus, we recommend that your Conjugated Saccharide and Saccharide Content (b) (4) assays serve as control for Total Saccharide, (b) (4) saccharide and conjugate amounts (b) (4) formulation and storage and any unforeseen issues that may occur. Therefore, the measurement of (b) (4) saccharide and conjugates at the DP level are not redundant as you state on page 19 of your IR response. Please include the Conjugated Saccharide Content and (b) (4) Saccharide Tests in your Drug Product Release Tests Panel. Please acknowledge.

IR COMMENT (5 March 2021): Please provide updated Stability Specification ranges for the Saccharide Content and Conjugated Saccharide Assays based upon a statistical analysis of your current data and stability projection estimates.

We recommend that you reevaluate your Saccharide Content and Conjugated Saccharide Content tests specifications after accumulation of a minimum of (b) (4) commercial batches to evaluate the process capability and estimate specification limits. Please acknowledge.

Merck's Response (12 March 2021): Merck acknowledges and commits to reevaluate Saccharide Content and Conjugated Saccharide Content specifications when data from a statistically relevant amount of batch data and real time stability data are available to

evaluate the process capability and estimate specification limits (e.g. minimum of (b) (4) commercial batches).

Response: We concur with the company's response.

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment (JC)

I defer to DMPQ

3.2.A.2 Adventitious Agents Safety Evaluation (JC)

No primary origin animal-derived raw materials are used in the manufacture of Pneumococcal Polysaccharides (PnPs), CRM197 Carrier Protein, Monovalent Bulk Conjugates (MBC), Aluminum Phosphate Adjuvant (APA) or DP. (b) (4)

(b) (4), is used in the manufacture of PnPs during the (b) (4) process. During the manufacturing process of CRM197 (b) (4) used in the manufacturing process. (b) (4)

(b) (4) used in the manufacture of PnPs meets is produced using (b) (4)

(b) (4) used in the manufacture of CRM197 is produced using (b) (4)

(b) (4) in MBC manufacture is in compliance with (b) (4)

Additionally, controls are in place throughout the manufacturing process of V114 including, environmental controls, (b) (4) testing of vaccine bulk and bulk intermediates.

Reviewer Assessment (JC)

No deficiencies identified.

3.2.A.3 Novel Excipients

(JC) There are no novel excipients in the DP.

3.2.R Regional Information (USA)

❑ Executed Batch Records (JC)

Master and Executed Batch Records were reviewed for the manufacturing process from polysaccharide (b) (4) through to drug product formulation and fill for serotypes 19A

and 33F. The Serotype 19A records were representative of the (b) (4) based and Serotype 33F representative of the (b) (4) manufacturing processes. The Executed Batch Records were compared to the Master Batch Records to establish if changes had been incurred through the manufacturing process development between the institution of the reviewed Executed versus the Master Batch Records. (b) (4) items were identified. The company was issued an IR on 2 April 2021 to address the identified issues. The company's response was received on 12 April 2021. The IR, Merck's responses, and reviewer's assessment are shown below:

COMMENT 2A: In BR_MBC_19A_MOD3G_0001100381 the CRM to CRM-UF-FR processing window is (b) (4) (page 92 of 124). The time-window defined in the recorded data is (b) (4) which adds up to (b) (4). The calculated actual time recorded is (b) (4), however the (b) (4) is crossed out and the correction is (b) (4). This is marked as an entry error, and a comment states that the "Proven acceptable range of (b) (4) not exceeded as per 56221-2018-TC-0611 Rev01 Technical Communication for V114 (b) (4)". Per 3.2.S.2.2 Description Of Manufacturing Process and Process Controls (MBC) the listed accumulated time for this process is (b) (4). The (b) (4) designated time allotment was exceeded. The submitted master batch records have the same (b) (4) processing window time limit. Please explain how exceeding the processing window by (b) (4) is allowed and provide 56221-2018-TC-0611 Rev01 Technical Communication for V114 (b) (4), all deviation reports for this MBC Batch, and any related CAPAs.

Merck's Response (12 April 2021): This procedure is covered by ADMIN905 (SOP-11100) Vaccine IPT Batch Record Control and Review. If there is data supporting the excursion a note is added. Additionally, Scientific Problem Solving (SPS) exercise is performed to review potential root cause(s). A CAPA (200877759) was filed after (4/7) the IR was submitted (4/2) to address timely addition of the note in the batch records. Deviation 200776887 200776888 appears to record the late entry of the note. The note in the batch records referenced document 56221-2018-TC-0044, which instructs the technician to contact the team lead in the case of exceeding time limits.

The applicant directs to 3.2.S.2.6 MANUFACTURING PROCESS DEVELOPMENT - PROCESS CHARACTERIZATION - PROCESSING TIMES (MBC). On page 27 there is a listing of lab scale processing time studies derived process times. The CRM processing time, listed in Table 39, shows (b) (4) CRM197 to CRM197 (b) (4) time of (b) (4). Scientific Problem Solving (SPS) exercise is performed to review potential root cause. If the PAR is exceeded a deviation is raised. The PAR was not exceeded.

COMMENT 2B: In BR_MBC_19A_MOD5M_0001100381, page 31 of 62 (step 10.9) the (b) (4) time is not recorded. According to the comment on the page the (b) (4)

instructs the operator “(b) (4)”. On page 34 of 62, step (b) (4) time is recorded. Please explain how you are able to control the (b) (4) process if specific time points are not recorded. Please provide any related deviation reports.

Merck’s Response: The company states that the recording referenced in step (b) (4) the start time is not always required. This start time records the time at which the (b) (4). In the case of batch (b) (4) here the (b) (4) was already achieved prior to (b) (4). As (b) (4)

Since the (b) (4) was reached prior to (b) (4) there was no requirement to log the (b) (4).

COMMENT 2C: *In BR_MBC_19A_MOD5M_0001100381, page 58 of 62 you report the (b) (4) for Serotype 19A is (b) (4). The time recorded for batch (b) (4). The batch record states that the process lead, or designee must be contacted in the event that the time is exceeded. While the time was exceeded, there is no indication that the lead was contacted, only that the PAR was not exceeded. Please define PAR and explain how it supersedes the allowable processing window defined in your batch record. Please include the criteria used to indicate that the process time for (b) (4) was not exceeded, the risk to the product for the time exceeded, and the decision process that allowed for continuation of the batch.*

Merck’s Response: PAR is defined as the Proven Acceptable Range. There was a delay in timely addition of the note to the batch records. While the note did not describe that the lead was contacted, it is implied. CAPA 200877759 was initiated that instructs for timely addition of these notes into the batch record. Section 3.2.S.2.6 MANUFACTURING PROCESS DEVELOPMENT - PROCESS CHARACTERIZATION - PROCESSING TIMES (MBC) was references for the PAR governing stage 19A (b) (4). Similar to the response in 2A, in the listed section, Table 50 of that document lists the operating range for this step to be (b) (4). The PAR was not exceeded, and the process intermediate stability is supported.

COMMENT 2D: *In BR_MBC_19A_MOD6NOPQ_0001100381, (page 17 of 396) (b) (4), there is a note in the lower margin that appears to indicate that when the analyst was instructed to (b) (4) was not present. It is not clear how this situation was corrected. The master batch records do not include a (b) (4). Please clarify how (b) (4) is controlled at this step. Please describe the*

process used to correct the situation including but not limited to any deviation reports, CAPA, and change controls related to this event.

Merck's Response: The (b) (4)

Deviation QN #200770064 documented the situation and CAPA QN#200774654. The CAPA removed the instruction to (b) (4)

The batch record was updated through change control via document TR ID 706268.

COMMENT 2E: *In BR_MBC_19A_MOD6NOPQ_0001100381 P2- MBC* (b) (4)

page 246 of 396 Step (b) (4)

A note in the margin states that the allowable range is incorrectly listed in the instructions and should be (b) (4), page 6 of 26 (V25.0). The master batch records do not list any (b) (4) or allowable range. Please provide (b) (4) and related documents; and explain and justify not including the specified (b) (4) and allowable range in the master batch records.

Merck's Response: While reference to the (b) (4) has been removed from the Master Batch Records instructions referenced to document (b) (4) on page 162 of 396, where the instruction to (b) (4), is maintained at (b) (4) is shown. The (b) (4) is also recorded when the (b) (4) is generated as shown on page 128 of 396 of the batch records. The (b) (4) is adequately monitored.

Reviewer Assessment: (JC) All IR questions, 2A through 2E, were adequately addressed.

❑ **Method Validation Package**

All method validation information included in the section were reviewed along with validation summaries presented in Sections 3.2.S.2.5 Process Validation and/or Evaluation (DS), 3.2.S.4.3 Validation of Analytical Procedures (DS), 3.2.P.3.5 Process Validation and/or Evaluation (DP), and 3.2.P.5.3 Validation of Analytical Procedures (DP). See review of those sections for details.

❑ **Combination Products (JC)**

The V114 DP is supplied as a prefilled syringe, which qualifies as a combination product. The syringe systems are delivered sterile, clean, and ready to be filled. The components are manufactured by (b) (4).

Device Risk Management Files (DRMF) are compliant to ISO (b) (4) and includes device risk management plan, hazards and harms list, device risk analyses, and a device risk management report. Processes to obtain relevant production and post-production information for maintenance of the DRMF are described in the supplier quality agreements. Post marketing safety surveillance information will be monitored. Based on the Sponsor's risk management, it was concluded that all residual risks are acceptable, and the drug-device combination product is safe and effective for its intended use.

The syringe device was subject to validation activities performed by (b) (4). The purpose of the validation was to demonstrate that the analytical method for analysis by (b) (4) is suitable for its intended use in evaluating the container closure integrity of V114 filled 1.5 mL syringes. Predetermined Acceptance Criteria were established. The criteria were met for precision, intermediate precision, repeatability, and range.

Purchasing controls are in place. The suppliers are evaluated for capability to provide that the product meets with specifications, including review of results of regulatory surveillance, consideration of historical experience with the supplier, due diligence assessment visit, and execution of Quality Agreements with the supplier. Audits are performed as part of the quality assessment. The quality agreement includes a change notification clause requiring all changes at the supplier or contract manufacturer to be notified to the Sponsor for assessment.

A Corrective and Preventative Actions (CAPA) system is part of the Sponsor's Quality Management System (QMS). Procedures re in place to evaluate deviations, customer complaints and observations from internal audits. Actions to correct and prevent recurrence are identified where appropriate. Adverse Events and Product Quality Complaints are investigated.

Reviewer's Assessment: (JC)

No deficiencies were identified.

□ Comparability Protocols (JC)

There are no comparability protocols.

Other eCTD Modules**Module 1****A. Environmental Assessment or Claim of Categorical Exclusion**

(JC) Merck & Co., Inc. has requested a categorical exclusion from the requirements to prepare an Environmental Assessment under 21 CFR §25.31(c). The BLA for Pneumococcal 15-valent Conjugate Vaccine [CRM197 Protein], (b) (4) meets the requirements of a categorical exclusion under this CFR section because the intended new vaccine consists of materials that occur naturally in the environment and manufacture or use of the vaccine will not alter significantly the concentration or distribution of the substance, its metabolites or degradation products in the environment.

B. Labeling Review**Full Prescribing Information (PI):****Carton and Container Label:**

(JC) The label and carton information were matched to information contained in the dossier. There was discussion concerning the non-proprietary name. In order to be consistent with recent polysaccharide conjugate vaccines the non-proprietary name will be listed as Pneumococcal 15 valent Conjugate Vaccine. There was a discrepancy concerning the amount of CRM₁₉₇ per dose. Table 1 in 3.2.P.1 DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT reported CRM₁₉₇ to be present at (b) (4) mcg/dose. This concentration did not match with the range calculated from DP release specifications. On 23 April 2021 the labeling committee sent an IR (125741/0.31) requesting clarity concerning the quantity per dose of CRM₁₉₇. Merck's response was received 30 April 2021. The table was corrected to reflect the accurate amount of CRM₁₉₇ at approximately 30 mcg per 0.5mL dose. The amount must be referred to as approximate due to the DS specification range of CRM₁₉₇ in each conjugate. Additional modifications were made to Table 1 to clarify composition. The (b) (4) column, which referred to composition per mL, was removed to prevent confusion. The L-Histidine and Sodium Chloride quantities have been amended to milligrams (mg) from millimolar (mM).

Reviewer Assessment:

The label and carton language are acceptable.

Modules 4 and 5**Analytical Procedures and Validation of Analytical Procedures for Assessment of Clinical and Animal Study Endpoints**

(MA)

1) Clinical studies and efficacy endpoints:

Study V114-019 (Pivotal study):

Among the 6 phase 3 studies, study V114-019 is the pivotal study. In this study, immunogenicity of V114 was compared to that of Prevnar 13™ in pneumococcal vaccine-naïve adults ≥50 years of age.

Primary efficacy objectives of the study:

- To compare the serotype-specific OPA geometric mean titers (GMTs) at 30 days postvaccination with V114 versus Prevnar 13™. The first hypothesis for this objective was that V114 is noninferior to Prevnar 13™ as measured by the serotype specific OPA GMTs for 13 shared serotypes at 30 days postvaccination. V114 met noninferiority criteria for this objective because the lower bound of the 95% confidence interval (CI) of the estimated OPA GMT ratio (V114/Prevnar 13™) was >0.5 for all shared serotypes. The second hypothesis for this objective was that V114 is superior to Prevnar 13™ as measured by serotype specific OPA GMTs for 2 unique serotypes in V114 at 30 days postvaccination. V114 met the superiority criterion for this objective because the lower bound of the 95% CI of the estimated OPA GMT ratio (V114/Prevnar 13™) was >2.0 for both the unique serotypes.
- To compare serotype-specific proportions of participants with a ≥4-fold rise from prevaccination to 30 days postvaccination for OPA responses for the 2 unique serotypes in V114 for participants administered V114 versus participants administered Prevnar 13™. The hypothesis for this objective was that V114 is superior to Prevnar 13™ for the 2 unique serotypes in V114 as measured by proportions of participants with a ≥4-fold rise from prevaccination to 30 days postvaccination for serotype-specific OPA responses. V114 met superiority criteria for this objective because the lower bound of the 2-sided 95% CI of the difference in percentages [V114-Prevnar 13™] for both the unique serotypes was >10 percentage points.

Secondary efficacy objectives of the study:

- To compare the serotype 3 OPA GMT at 30 days postvaccination with V114 versus Prevnar 13™. The hypothesis for this objective was that V114 is superior to Prevnar 13™ as measured by the serotype 3 OPA GMTs at 30 days postvaccination. V114 met superiority criteria for this objective because the lower bound of the 95% CI of the estimated OPA GMT ratio (V114/Prevnar 13™) for serotype 3 was >1.2.

- To compare proportions of participants with a ≥ 4 -fold rise from prevaccination to 30 days postvaccination for the serotype 3 OPA responses for participants administered V114 versus participants administered Prevnar 13™. The hypothesis for this objective was that V114 is superior to Prevnar 13™ for serotype 3 as measured by proportions of participants with a ≥ 4 -fold rise from prevaccination to 30 days postvaccination for OPA responses. V114 met superiority criteria for this objective because the lower bound of the 2-sided 95% CI of the difference in percentages [V114-Prevnar 13™] for serotype 3 was >0 percentage point.

- To evaluate the serotype-specific IgG Geometric Mean Concentrations (GMCs) at 30 days postvaccination with V114 compared with Prevnar 13™. No hypothesis was tested for this objective. Overall, between-group comparisons of IgG GMCs at 30 days postvaccination were consistent with the primary analysis of OPA GMTs.

- To evaluate the serotype-specific Geometric Mean Fold Rises (GMFRs) and proportions of participants with a ≥ 4 -fold rise from prevaccination to 30 days postvaccination for both OPA and IgG responses for participants administered V114 and separately for participants administered Prevnar 13™. No hypothesis was tested for this objective. Serotype-specific GMFRs and proportions of participants with a ≥ 4 -fold rise from prevaccination to 30 days postvaccination for both OPA responses and IgG responses were generally comparable in both intervention groups for the shared serotypes and higher in the V114 group compared with the Prevnar 13™ group for serotype 3 and the 2 serotypes unique to V114.

Study V114-020 (Lot Consistency):

In this study, immunogenicity of three different V114 lots were evaluated in pneumococcal vaccine-naïve adults ≥ 50 years of age.

Primary immunogenicity endpoint:

- To compare the serotype-specific OPA GMTs at 30 days postvaccination across 3 different lots of V114. The hypothesis for this objective was that all 3 lots of V114 are equivalent as measured by the serotype specific OPA GMTs for 15 serotypes in V114 at 30 days postvaccination. V114 met equivalence criteria for this objective because lower bound of the 95% CI of the OPA GMT ratios for each pairwise lot-to-lot comparison were within 0.5 to 2.0 for all 15 serotypes in V114.

Secondary immunogenicity endpoints:

- To evaluate the serotype-specific IgG GMCs at 30 days post vaccination compared across the 3 different lots of V114 and combined lots of V114 compared to Prevnar 13™. No hypothesis was tested for this endpoint. Between-group comparisons of IgG GMCs at 30 days postvaccination with V114 (Lot 1, Lot 2, Lot 3) were consistent with the primary analysis of OPA GMTs. Also, serotype-specific IgG GMCs at 30 days postvaccination were comparable in the V114 (combined lots) and Prevnar 13™ intervention groups for the 13 shared serotypes, and higher following administration of V114 compared with Prevnar 13™ for the 2 serotypes unique to V114.
- To evaluate the serotype-specific GMFRs and proportions of participants with a ≥ 4 -fold rise from prevaccination to 30 days postvaccination for both OPA and IgG responses separately across 3 different lots of V114. No hypothesis was tested for this endpoint. OPA and IgG antibody responses (GMFRs and proportions of participants with a ≥ 4 -fold rise from prevaccination to 30 days postvaccination with V114) were generally comparable across the 3 V114 lots for all 15 serotypes in V114.

Study V114-017 (Immunocompetent adults 18 to 49 years of age with at-risk conditions):

In this study, immunogenicity of a single dose of V114 in pneumococcal vaccine-naïve, immunocompetent adults 18 to 49 years of age with or without risk factors for pneumococcal disease followed by sequential administration of licensed 23-valent polysaccharide (PPV23) vaccine PNEUMOVAX™23, 6 months later was evaluated. Control arm of the study included those who were administered Prevnar 13™ instead of V114.

Primary immunogenicity endpoint:

- To evaluate the serotype specific OPA GMTs at 30 days postvaccination with V114 and Prevnar 13™ within each vaccination group separately. No hypothesis was tested for this endpoint. V114 was immunogenic in pneumococcal vaccine-naïve, immunocompetent adults 18 to 49 years of age with or without risk factors for pneumococcal disease as assessed by OPA GMTs at 30 days postvaccination for all 15 serotypes contained in the vaccine. Prevnar 13™ was immunogenic as assessed by OPA GMTs at 30 days postvaccination for all 13 serotypes contained in the vaccine.

Secondary immunogenicity endpoints:

- To evaluate the serotype-specific IgG GMCs at 30 days postvaccination with V114 and Prevnar 13™ within each vaccination group separately. No hypothesis was tested for this endpoint. V114 was immunogenic in as assessed by IgG GMCs at 30 days postvaccination for all 15 serotypes contained in the vaccine. Prevnar 13™ was immunogenic as assessed by IgG responses at 30 days postvaccination for all 13 serotypes contained in the vaccine.

- To evaluate the serotype-specific GMFRs and proportions of participants with a ≥ 4 -fold rise from prevaccination to 30 days postvaccination for both OPA and IgG responses for participants administered V114 and for participants administered Prevnar 13™ within each vaccination group separately. No hypothesis was tested for this endpoint. V114 was immunogenic in as assessed by the serotype-specific GMFRs and proportions of participants with a ≥ 4 -fold rise from prevaccination to 30 days postvaccination for both OPA and IgG responses participants administered V114 for all 15 serotypes contained in the vaccine. Prevnar 13™ was immunogenic for all 13 serotypes contained in the vaccine.

- To evaluate the serotype-specific (1) OPA GMTs and IgG GMCs at 30 days postvaccination with PNEUMOVAX™23 (Month 7), (2) GMFRs and proportions of participants with a ≥ 4 -fold rise from prevaccination to 30 days postvaccination with PNEUMOVAX™23 (Month 7) for both OPA and IgG responses, (3) GMFRs and proportions of participants with a ≥ 4 -fold rise from prevaccination with PNEUMOVAX™23 (Month 6) to 30 days postvaccination with PNEUMOVAX™23 (Month 7) for both OPA and IgG responses for participants administered V114 and separately for participants administered Prevnar 13™ 6 months before receipt of PNEUMOVAX™23. No hypothesis was tested for this endpoint. V114 or Prevnar 13™ followed by PNEUMOVAX™23 was immunogenic for all 15 serotypes as assessed by serotype specific OPA GMTs and IgG GMCs at 30 days postvaccination with PNEUMOVAX™23. PNEUMOVAX™23 elicited an immune response for serotypes 22F and 33F at 30 days postvaccination with PNEUMOVAX™23 in the Prevnar 13™ group. Also, V114 was immunogenic for all 15 serotypes contained in the vaccine as assessed by serotype-specific OPA GMFRs and IgG GMFRs and the proportions of participants with a ≥ 4 -fold rise in OPA titers and IgG concentrations from prevaccination with PCV to 30 days postvaccination.

Study V114-018 (Immunocompromised adults ≥ 18 years of age):

In this study, immunogenicity of a single dose of V114 in adults 18 years of age or older infected with human immunodeficiency virus (HIV) who did not receive a pneumococcal

vaccine prior to study entry was evaluated. Control arm of the study included those who were administered Prevnar 13™ instead of V114.

Primary immunogenicity endpoint:

- To evaluate the serotype-specific OPA GMTs and IgG GMCs at 30 days postvaccination with V114 and Prevnar 13™ within each vaccination group separately. No hypothesis was tested for this endpoint. V114 was immunogenic in pneumococcal vaccine-naïve adults infected with HIV as assessed by OPA GMTs and IgG GMCs for all 15 serotypes contained in the vaccine. Prevnar 13™ was immunogenic as assessed by OPA GMTs and IgG GMCs for all 13 serotypes contained in the vaccine.

Secondary immunogenicity endpoint:

- To evaluate the serotype-specific OPA GMTs and IgG GMCs at 30 days postvaccination with PNEUMOVAX™23 (week 12) for participants administered V114 and separately for participants administered Prevnar 13™ 8 weeks before receipt of PNEUMOVAX™23. No hypothesis was tested for this endpoint. Serotype-specific OPA GMTs and IgG GMCs at 30 days postvaccination with PNEUMOVAX™23 were generally comparable with those observed at 30 days postvaccination with PCV in the V114 group for all 15 serotypes and in the Prevnar 13™ group for all 13 serotypes contained in the vaccine. PNEUMOVAX™23 elicited an immune response for serotypes 22F and 33F at 30 days postvaccination with PNEUMOVAX™23 in the Prevnar 13™ group.

Study V114-016 (Sequential administration of V114 followed by PPV23):

In this study, immunogenicity of a single dose of V114 in adults followed by PNEUMOVAX™23 1 year later in healthy adults aged ≥50 years was evaluated. Control arm of the study included those who were administered Prevnar 13™ instead of V114.

Primary immunogenicity endpoint:

- To evaluate the serotype-specific OPA GMTs at 30 days postvaccination with PNEUMOVAX™23 (Month 13) for participants administered V114 compared with participants administered Prevnar 13™ 12 months before receipt of PNEUMOVAX™23. No hypothesis was tested for this endpoint. Serotype-specific OPA GMTs at 30 days following vaccination with PNEUMOVAX™23 (Month 13) were generally comparable between participants administered V114 or Prevnar 13™ 12 months prior to receipt of PNEUMOVAX™23 for all 15 serotypes in V114.

Secondary immunogenicity endpoints:

- To evaluate the serotype-specific IgG GMCs at 30 days postvaccination with PNEUMOVAX™23 (Month 13) for participants administered V114 compared with participants administered Prevnar 13™ 12 months before receipt of PNEUMOVAX™23. No hypothesis was tested for this endpoint. Between-group comparisons of IgG GMCs at 30 days following vaccination with PNEUMOVAX™23 (Month 13) were consistent with the primary analysis of OPA GMTs.

- To evaluate the serotype-specific (1) OPA GMTs and IgG GMCs at 30 days postvaccination and (2) GMFRs and proportions of participants with a ≥ 4 -fold rise from prevaccination to 30 days postvaccination for both OPA and IgG responses for participants administered V114 and separately for participants administered Prevnar 13™. No hypothesis was tested for this endpoint. Serotype-specific OPA GMTs and IgG GMCs were generally comparable across intervention groups for the 13 shared serotypes, and higher for the 2 serotypes unique to V114 following administration of V114 compared with Prevnar 13™.

- To evaluate the serotype-specific (1) OPA GMTs and IgG GMCs at 12 months postvaccination (Month 12) and (2) GMFRs and proportions of participants with a ≥ 4 -fold rise from prevaccination to 12 months postvaccination (Month 12) for both OPA and IgG responses for participants administered V114 and separately for participants administered Prevnar 13™. No hypothesis was tested for this endpoint. Serotype-specific OPA GMTs and IgG GMCs at 12 months following vaccination with PCV (Month 12) were generally comparable across intervention groups for the 13 shared serotypes, and higher for the 2 serotypes unique to V114 following administration of V114 compared with Prevnar 13™.

- To evaluate the serotype-specific (1) OPA GMTs and IgG GMCs at 30 days postvaccination with PNEUMOVAX™23 (Month 13), (2) GMFRs and proportions of participants with a ≥ 4 -fold rise from prevaccination to 30 days postvaccination (Month 13) with PNEUMOVAX™23 for both OPA and IgG responses, and (3) GMFRs and proportions of participants with a ≥ 4 -fold rise from prevaccination with PNEUMOVAX™23 (Month 12) to 30 days postvaccination with PNEUMOVAX™23 (Month 13) for both OPA and IgG responses for participants administered V114 and separately for participants administered Prevnar 13™ 12 months before receipt of PNEUMOVAX™23. No hypothesis was tested for this endpoint. V114 was immunogenic for all 15 serotypes contained in the vaccine as assessed by serotype-specific OPA GMFRs and the proportions of participants with a ≥ 4 -fold rise in OPA titers from prevaccination with PCV (Day 1) to 30 days and 12 months postvaccination.

Study V114-021 (Concomitant administration of influenza vaccine):

In this study, immunogenicity of a single dose of V114 when administered concomitantly with quadrivalent influenza vaccine QIV in healthy adults 50 years of age or older was evaluated.

Primary immunogenicity endpoint:

- To compare the serotype-specific OPA GMTs at 30 days postvaccination with V114 administered concomitantly with QIV versus V114 administered non concomitantly with QIV. The hypothesis for this objective was that V114 administered concomitantly with QIV is **noninferior** to V114 administered non concomitantly with QIV as measured by the serotype specific OPA GMTs at 30 days postvaccination with V114. V114 met noninferiority criteria for this objective because the lower bound of the 2-sided 95% CI of the OPA GMT ratio was >0.5 for all serotypes.

Secondary immunogenicity endpoint:

- To evaluate the serotype-specific IgG GMCs at 30 days postvaccination with V114 administered concomitantly with QIV compared with V114 administered non concomitantly with QIV. No hypothesis was tested for this endpoint. Between-group comparisons of IgG GMCs at 30 days postvaccination with V114 were consistent with the primary analysis of OPA GMTs.
- Within each vaccination group, to evaluate the serotype-specific GMFRs and proportions of participants with a ≥ 4 -fold rise from baseline (prevaccination with V114) to 30 days postvaccination with V114 for both OPA and IgG responses for participants administered V114 concomitantly with QIV and participants administered V114 non concomitantly with QIV. No hypothesis was tested for this endpoint. OPA GMFRs and proportions of participants with a ≥ 4 -fold rise in OPA, and IgG responses from baseline to 30 days postvaccination with V114 were generally comparable between the concomitant and non-concomitant groups. There was a trend toward lower IgG GMFRs in the concomitant group compared with the non-concomitant group.

Study V114-007 (Administration of V114 in adults with prior PNEUMOVAX™23 vaccination):

This is a Phase 2 study to investigate the safety and immunogenicity of V114 when administered to adults ≥ 65 years of age who had received PNEUMOVAX™23 one year

ago. Control arm of the study included those who were administered Prevnar 13™ instead of V114.

Primary immunogenicity endpoint:

-To evaluate the serotype-specific IgG GMCs prior to and at 30 days post vaccination with V114 and Prevnar 13™ for the 13 shared pneumococcal serotypes contained both vaccines and the 2 serotypes unique to V114. Also, the GMFR from baseline and the percentage of subjects who achieved at least a 4-fold-raise in serotype-specific IgG responses from baseline were assessed. No hypothesis was tested for this endpoint. Baseline GMCs were similar across the 2 vaccination groups for each of the 15 pneumococcal serotypes. Similarly, the IgG GMCs, GMFRs, and percentages of subjects with ≥4-fold-raise at 30 days postimmunization were comparable for the 13 shared serotypes between the V114 and Prevnar 13™ vaccinees. For the two serotypes unique to V114, the IgG GMCs, GMFRs, and percentages of subjects with ≥4-fold-raise at 30 days postimmunization were generally higher for subjects administered V114 compared with those administered Prevnar 13™.

Secondary immunogenicity endpoint:

-To evaluate the serotype-specific OPA GMTs prior to and at 30 days post vaccination with V114 and Prevnar 13™ for the 13 shared pneumococcal serotypes contained both vaccines and the 2 serotypes unique to V114. No hypothesis was tested for this endpoint. Baseline GMTs were similar across the 2 vaccination groups for each of the 15 pneumococcal serotypes. Similarly, the GMTs, GMFRs, and percentages of subjects with ≥4-fold-raise at 30 days postimmunization were comparable for the 13 shared serotypes between the V114 and Prevnar 13™ vaccinees. For the two serotypes unique to V114, the GMTs, GMFRs, and percentages of subjects with ≥4-fold-raise at 30 days postimmunization were generally higher for subjects administered V114 compared with those administered Prevnar 13™.

Exploratory immunogenicity endpoint:

- To evaluate the immunogenicity (as measured by the Pn ECL assay and the MOPA-4 assay) of V114 and Prevnar 13™ by time since receipt of PNEUMOVAX™23 (1 to 3 years versus >3 years) for each age cohort (65 to 74 years of age versus ≥75 years of age). No hypothesis was tested for this endpoint. In general, higher IgG and OPA antibody responses were observed in the older age group with longer time since PNEUMOVAX™23 and primarily in the V114 group. However, the results remained descriptive due to small sample size.

- To compare the immunogenicity (as measured by the MOPA-4 and Pn ECL assays) at Day 30 postvaccination in recipients of V114 and Prevnar 13™ for the 13 shared pneumococcal serotypes contained in both vaccines and the 2 serotypes unique to V114. No hypothesis was tested for this endpoint. Overall, both estimated IgG GMCs and the estimated OPA GMTs at 1-month postvaccination were comparable between recipients of V114 and Prevnar 13™ for all 13 shared serotypes. For the 2 serotypes unique to V114, Day 30 estimated IgG GMCs were at least 2-fold higher and Day 30 estimated OPA GMTs were at least 3-fold higher in the V114 group vs. the Prevnar 13™ group.

Sensitivity analysis of primary and key secondary OPA endpoints of studies V114-016, V114-017, V114-019, and V114-020 with and without the removal of IK positive samples:

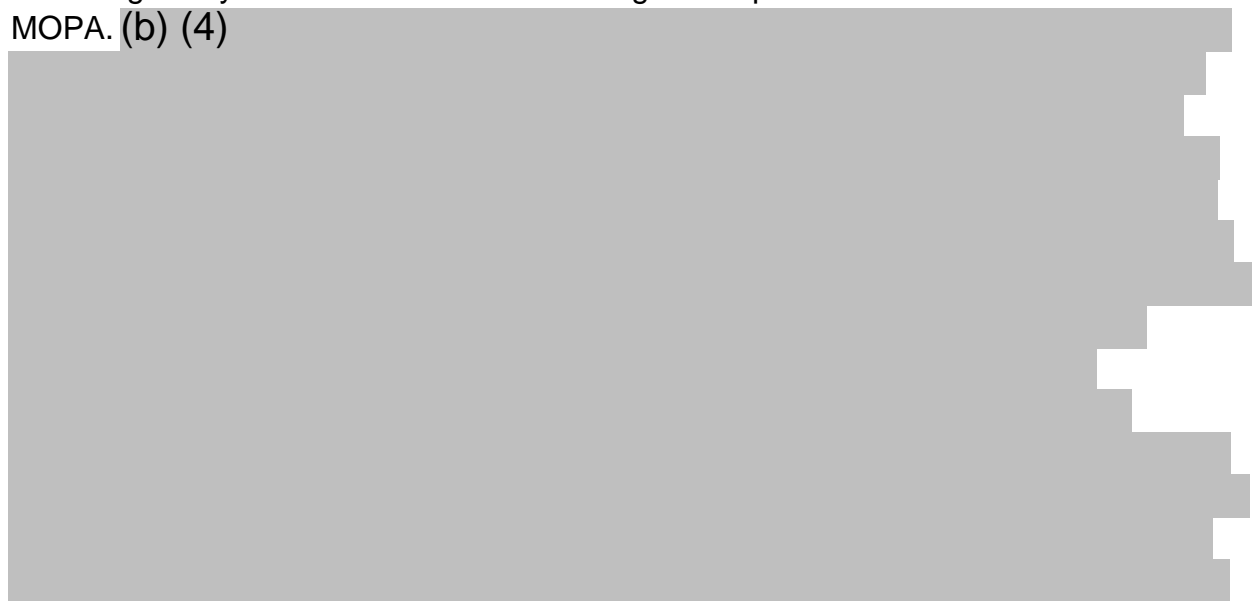
The MOPA-4 used to assess the efficacy of V114 includes the evaluation of all samples for (b) (4) independent of antibodies targeting vaccine serotypes in an (b) (4) assay (b) (4). The primary source of (b) (4) in serum samples is the use of antibiotics during the trial period by the subjects. During the review of IND-MF-(b) (4), Merck indicated that while the (b) (4) positivity rate was within the expected range for studies V114-021 and V114-018, the positivity rate increased to markedly higher levels in studies V114-016, V114-017, V114-019, and V114-20. According to Merck, the higher than expected rate of (b) (4) rate in the samples from these studies was likely due to a reagent change and they expressed their intent to evaluate the MOPA results from these studies without removing the (b) (4) positive samples. In support of this decision, Merck indicated very low self-declared antibiotic usage among the subjects participating to these four studies. CBER did not accept the efficacy assessment using all clinical samples and asked Merck to improve the (b) (4) assay and re-test the samples that were positive in (b) (4) assay (b) (4). After several rounds of review, the modified version of (b) (4) assay (b) (4) was found to be appropriate for the intended use by CBER. Despite the re-testing of the samples from studies V114-016, V114-017, V114-019, and V114-20 with (b) (4) assay (b) (4), the evaluation of MOPA-related endpoints presented in the CSRs for these studies were based on results from all available MOPA data, regardless of (b) (4) status. However, Merck also submitted a sensitivity analysis of the primary and key secondary MOPA endpoints for studies V114-016, V114-017, V114-019, and V114-020 that include MOPA data only for samples testing negative in the modified (b) (4) test (Sensitivity Analysis of Primary and Key Secondary OPA Endpoints of Studies V114-016, V114-017, V114-019, and V114-020 Using an (b) (4) Test as a Precondition for OPA Testing). The review of these data indicated that the primary and key secondary MOPA endpoints evaluated with and without removal of (b) (4) positive samples were highly comparable.

On June 2, 2021 (amendment 35), the applicant submitted additional analysis of samples from studies V114-020, V114-019, V114-007, and V114-017 in response to IR sent by clinical review team to Merck on May 26, 2021. The clinical review team had requested the applicant to submit shell tables with demographic details of participants and safety analysis in addition to immunogenicity analysis using only (b) (4) negative samples for studies V114-020, V114-019, V114-007, and V114-017. In addition to submitting the requested shell tables, the applicant also indicated that they had discovered an error in the calculation of GMFR or 4-fold rise analyses for studies V114-017, V114-019, and V114-020. The applicant indicated that in the original analysis, all time 0 samples were used instead of using only (b) (4) negative samples. In amendment 35, the applicant submitted tables for studies V114-017 and V114-019 with repeated 4-fold analysis using only (b) (4) negative samples from time 0. Table D of study V114-017 and V114-019 documents included the updated percentages of subjects achieving 4-fold rise in MOPA titers. Comparison of these data with the original Statistical Report for the (b) (4) Sensitivity Analyses submitted to amendment 1 indicated that not all serotypes were effected from the reanalysis and the differences in the percentage of subjects achieving 4-fold rise for those serotypes that were effected remained less than 0.5%. Thus, this reanalysis did not change the overall conclusion of the immunogenicity responses for these studies. The applicant indicated that they plan to submit updated Statistical Report for the (b) (4) Sensitivity Analyses to the BLA by June 16, 2021.


2) MOPA SOP and Validation

2.1) MOPA SOP (*Document name: "Method, VSDVAC 37" Version 1, May 16, 2017*).

Immunogenicity of V114 was assessed using a multiplexed version of the OPA called MOPA. (b) (4)



(b) (4)



4) Immunogenicity evaluation of V114 in animal studies under “Nonclinical Study Reports”

Immunogenicity of V114 was evaluated in (b) (4) rabbits and infant rhesus monkeys as part of pharmacodynamics studies under “4.2.1 Pharmacology” section. In additional animal studies, rats were immunized with different formations and doses of V114 preparations as part of “Toxicology” (4.2.3) studies. In all animal studies vaccine responses were assessed by measuring serum IgG antibody levels against vaccine PnPS in ECL assay. In addition, serum antibody responses were evaluated in MOPA assay in (b) (4) rabbit and infant rhesus monkey immunization studies. The ECL assay used in animal studies was near identical to those used in human studies. Antibodies bound to PnPS sport were detected using (b) (4) IgG Fc antibodies. Anti-human IgG Fc antibodies were used to detect rhesus monkey antibodies. Also, unlike in human ECL assay, the version used for animals did not include a reference standard. Instead, the ECL titer was calculated as the reciprocal of the linearly interpolated dilution corresponding to the cutoff value. Interpolation was performed using logarithmic scaling for ECL and the dilution. Titer was then obtained by back transforming the linearly interpolated dilution. The ECL used in animal studies was a qualified assay that was sufficient for the intended use. The MOPA assay used for (b) (4) rabbit and infant rhesus monkeys was identical to the assay used in human studies.

Immunogenicity of V114 formulations in (b) (4) Rabbits

The groups of (b) (4) rabbits were immunized with formulations of V114. Serum immune responses were assessed in ECL and MOPA assays. The ECL assay used in rabbit studies was near identical to those used in animal studies. In ECL assay, antibodies

bound to (b) (4) were detected using (b) (4) IgG Fc antibodies. Also, in ECL assay a reference standard was not used. Instead, the ECL titer was calculated as the reciprocal of the linearly interpolated dilution corresponding to the cutoff value. Interpolation was performed using logarithmic scaling for ECL and the dilution. Titer was then obtained by back transforming the linearly interpolated dilution. MOPA assay was identical to the assay used in human studies.

V114 was tested as:

- Study (b) (4)-14: 1.0 µg of each PnPS, with the exception of 6B at (b) (4), with (b) (4) of aluminum in a 0.25 mL volume. V114 formulations with (b) (4) were compared with each other ('V114 Formulation A' and 'V114 Formulation A (b) (4)', respectively). Each group of 8 (b) (4) rabbits received the vaccines on days 0 and 14. Serum was collected on days 0, 14, and 28.
- Study (b) (4)-16: The rabbits received one-fifth of a human dose of either V114 or Prevnar 13™ vaccine; (b) (4) of each PnPS, with the exception of 6B at (b) (4) with (b) (4) of aluminum in a 0.1 mL volume. V114 Formulation B was compared with Prevnar 13™; the V114 Formulation B in (b) (4)-16 included (b) (4), a non-toxic fragment of diphtheria toxin. Each group of 17 (b) (4) rabbits received the vaccines on days 0 and 14. Serum was collected on days 0, 14, and 28.
- Study (b) (4)-17: The rabbits received one-fifth of a human dose of either V114 or Prevnar 13™ vaccine; (b) (4) of each PnPS, with the exception of 6B at (b) (4), with (b) (4) of aluminum in a 0.1 mL volume. V114 Formulation B (Lot 1 and Lot 2) was compared with Prevnar 13™. Each group of 8 (b) (4) rabbits received the vaccines on days 0 and 14. Serum was collected on days 0, 14, and 28.

Results:

- Study (b) (4)-14: For this study Merck presented IgG titer ratio for V114 formulation A to V114 formulation (b) (4). For all V114 serotypes the ratio were higher than 1, suggesting that formulation A was more immunogenic.
- Study (b) (4)-16: Data were similar for both IgG responses and MOPA titers for 11 of the 13 serotypes. The IgG responses to the V114 Formulation B were less than the response to Prevnar 13™ for all 12 serotypes except for PnPS14. The MOPA titers were also generally low in rabbits immunized with V114 Formulation B, except for responses to PnPS14 and PnPS3.

- Study (b) (4)-17: The IgG and MOPA titer responses to the V114 Formulation B, Lot 2 was comparable to Lot 1. On the other hand, V114 Formulation B, Lot 2 IgG and MOPA titer responses were lower than the responses to Prevnar 13™ for all serotypes with the exception of PnS14 and PnPS7F.