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Division / Office	OVRR
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Review Completion Date / Stamped Date	
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Applicant	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Established Name	Pneumococcal 15-valent Conjugate Vaccine [CRM ₁₉₇ Protein], (b) (4) (V114)
Trade Name	VAXNEUVANCE [®]
Pharmacologic Class	Vaccine
Formulation, including Adjuvants, etc.	Suspension for injection, supplied as a single-dose prefilled syringe
Dosage Form and Route of Administration	Administer a 0.5 mL dose intramuscularly
Dosing Regimen	Single dose
Indication and Intended Population	For active immunization for the prevention of invasive pneumococcal disease caused by <i>Streptococcus pneumoniae</i> serotype (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F) in adults 18 years of age and older

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GLOSSARY

APA	aluminum phosphate adjuvant
BLA	biologics license application
CI	confidence interval
(b) (4)	(b) (4)
DOE	design of experiment
DP	drug product
DS	drug substance
ECL	electrochemiluminescence
(b) (4)	(b) (4)
(b) (4)	(b) (4)
IND	Investigational New Drug application
Merck	Merck Sharp & Dohme Corp.
MF	Master File
MOPA	Multiplexed Opsonophagocytic Killing Assay
RSD	relative standard deviation
SAP	statistical analysis plan
S.	<i>Streptococcus</i>
WHO	World Health Organization
(b) (4)	(b) (4)

1. Executive Summary

Merck Sharp & Dohme Corp. (Merck) submitted an original Biologics License Application (BLA) on November 17, 2020 for Pneumococcal 15-valent Conjugate Vaccine [CRM₁₉₇ Protein], (b) (4) (V114). V114 is a pneumococcal conjugate vaccine that contains 15 distinct pneumococcal capsular polysaccharides individually conjugated to the CRM₁₉₇ carrier protein originating from *Corynebacterium diphtheriae* C7. The proposed indication is for active immunization for the prevention of invasive pneumococcal disease caused by *Streptococcus (S.) pneumoniae* serotype (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F and 33F) in adults 18 years of age and older. V114 is a 0.5-mL suspension for injection (intramuscular administration only), administered as a single dose in adults.

This application includes

- a Validation Report of a (b) (4) method for identification and quantification of saccharide content in V114 Drug Product (DP) samples, and
- a Validation Report of a Conjugated Saccharide (b) (4) method for quantification of conjugated saccharide content in V114 DP samples.

These two validation reports were not reviewed previously, and thus this review memo focuses on the review of these two potency assays based on the validation reports submitted in Module 3.2.P.5.3 of BLA125741/0.1.

With respect to the validation of identity and saccharide content by (b) (4), based on results from the initial and the supplemental validation studies, the saccharide assay has

acceptable accuracy, specificity, linearity and precision. Robustness of the assay was only visually evaluated for trends in terms of bias and variability. According to an internal discussion, the product reviewer, Dr. Cipollo, considers the assay robust across the conditions tested. In the evaluation of laboratory equivalence, although the acceptance criteria for transfer from (b) (4) were determined solely based on statistical assumptions instead of scientific rationales, the product reviewer considers the acceptance criteria acceptable. The results from the equivalence study support the conclusion of equivalence between the (b) (4) laboratories.

With respect to the validation of conjugated saccharide (b) (4), based on results from the validation study, the conjugate saccharide assay has acceptable accuracy, specificity, linearity, precision, and robustness.

In validations of both saccharide and conjugate saccharide assays, some assay parameters were evaluated only for a subset of serotypes instead of all 15 serotypes. For example, robustness of the saccharide assay was evaluated for (b) (4), repeatability of the conjugate saccharide assay was evaluated for (b) (4) and robustness of the conjugate saccharide assay was evaluated for (b) (4). Similarly, laboratory equivalence of the saccharide assay was evaluated for (b) (4). The product reviewer considers such a reduced validation strategy to be sufficient.

To conclude, I consider both saccharide and conjugate saccharide assays adequate for their intended uses.

2. Clinical and Regulatory Background

Merck submitted a BLA on November 17, 2020 for V114. This submission summarizes the results from 7 clinical studies (1 Phase 2 study [V114-007] and 6 Phase 3 studies [V114-016, V114-017, V114-018, V114-019, V114-020, and V114-021]) conducted in adults ≥ 18 years of age. The results from these studies were used to support the use of V114 for active immunization for the prevention of invasive pneumococcal disease caused by *S. pneumoniae* serotype contained in the vaccine in adults 18 years of age and older. A comprehensive nonclinical program has been conducted with V114 to support its favorable benefit/risk profile.

The following documents regarding the validation of clinical assays were submitted in Module 5.3.1.4 of BLA125741/0.1 and BLA125741/0.4:

- Validation Statistical Report (b) (4) entitled “Validation of an ECL Method for the Detection of Antibodies to Pneumococcal Polysaccharide Serotypes 1, 5, 6A, 7F, 19A, 22F, and 33F (b) (4) ECL v2.0) in Human Serum”, dated July 14, 2017
- Validation Statistical Report (b) (4) entitled “Validation of an ECL Method for the Detection of Antibodies to Pneumococcal Polysaccharide Serotypes 3, 4, 6B, 9V, 14, 18C, 19F, and 23F (b) (4) ECL v2.0) in Human Serum”, dated July 14, 2017
- Bridging Report entitled “Bridging of the (b) (4) ECL v2.0 and (b) (4) ECL v2.0 Assays to the (b) (4) IgG (b) (4) and Determining the Pn ECL v2.0 Threshold Values Corresponding to (b) (4) Measured using the (b) (4) for Pneumococcal

Serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F”, dated September 20, 2017

- Validation Statistical Report (b) (4) entitled “Validation of a Multiplexed Opsonophagocytic Killing Assay (MOPA) for the Measurement of Antibodies Against *Streptococcus pneumoniae* Serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F”, dated February 19, 2019
- Qualification Report entitled “Qualification of the (b) (4) screen to support the multiplexed opsonophagocytic killing assay (MOPA) for the measurement of antibodies against *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F”, dated August 25, 2020.

The Validation Statistical Reports (b) (4) and (b) (4) were reviewed under Master File (MF)(b) (4) (MF(b) (4)), and statistical comments pertaining these two reports were sent to the applicant on December 19, 2017. The applicant responded to these statistical comments in MF(b) (4)/Amendment 3. Their responses were acceptable, and there were no additional statistical comments. We deemed both multiplex electrochemiluminescence-based detection assays (i.e. (b) (4) ECL v2.0 and (b) (4) ECL v2.0) validated for its intended use.

The Bridging Report and applicant’s responses to CBER comments pertaining this Bridging Report were reviewed under Investigational New Drug application (IND)(b) (4)/Amendments 6 and 11 (IND(b) (4) and IND(b) (4)). The applicant outlined the strategy for assigning (b) (4)

(b) (4). After discussion with the product reviewer, the review team considered Merck’s bridging method acceptable.

The Validation Statistical Report (b) (4) was reviewed under MF(b) (4) /Amendment 4 (MF(b) (4)). Per discussion with the product reviewer, we considered the MOPA validation acceptable for its intended use. The Qualification Report for (b) (4) was reviewed under MF(b) (4)/Amendment 15 (MF(b) (4)). Per discussion with the product reviewer, we considered the (b) (4) sufficiently qualified to be used for screening clinical samples.

Hence, this review memo focuses on the two potency assays based on the validation reports submitted in Module 3.2.P.5.3 of BLA125741/0.1, which have not been previously reviewed yet.

3. SOURCES OF DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

This statistical review focuses on the validation report of the (b) (4) method for identification and quantification of saccharide content in V114 DP samples and the validation report of the conjugated saccharide (b) (4) method for quantification of conjugated saccharide content in V114 DP samples submitted in Module 3.2.P.5.3 of BLA125741/0.1. Other supporting documents include Document 56085-2016-TR-0071^{(b) (4)} entitled “Technical Report for Validation of AP919.4136: Total Polysaccharide (Ps) (b) (4) for Pneumoconjugate Vaccine, V114, (b) (4) 17, JUN-

2017”, Document 56085-2017-TR-0028 REV 01 entitled “Technical Report for Supplemental Validation of AP919.4136: Total Polysaccharide (Ps) (b) (4) for Pneumoconjugate Vaccine, V114, (b) (4) 17, AUG-2018 REV 01” and Document AS-17-TT24-0008-QR entitled “Analytical Technology Transfer and Qualification Report for the Total Polysaccharide (Ps) (b) (4) for Pneumoconjugate Vaccine (V114) at (b) (4) submitted in Module 3.2.R of BLA125741/0.1, Document 05QYBW entitled “V114 Total PS (b) (4) Robustness Report” and Document 05QYBX entitled “V114 (b) (4) Robustness Report” submitted in Module 3.2.R of BLA125741/0.19.

4. REVIEW OF THE VALIDATION REPORT OF A (b) (4) METHOD FOR IDENTIFICATION AND QUANTIFICATION OF SACCHARIDE CONTENT IN V114 DP SAMPLES

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

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

(b) (4)

[Redacted text block]

5. REVIEW OF THE VALIDATION REPORT OF A CONJUGATED SACCHARIDE (b) (4)
[Redacted] METHOD FOR QUANTIFICATION OF CONJUGATED
SACCHARIDE CONTENT IN V114 DP SAMPLES

(b) (4)

[Redacted text block]

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

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

6. CONCLUSIONS

This review memo focuses on the review of two potency assays (i.e., a saccharide assay and a conjugate saccharide assay) based on the validation reports submitted in Module 3.2.P.5.3 of BLA125741/0.1.

With respect to the validation of identity and saccharide content by (b) (4), based on results from the initial and the supplemental validation studies, the saccharide assay has acceptable accuracy, specificity, linearity and precision. Robustness of the assay was only visually evaluated for trends in terms of bias and variability. According to an internal discussion, the product reviewer considers the assay robust across the conditions tested. In the evaluation of laboratory equivalence, although the acceptance criteria for transfer from (b) (4) were determined solely based on statistical assumptions instead of scientific rationale, the product reviewer considers the acceptance criteria acceptable. The results from the equivalence study support the conclusion of equivalence between the two laboratories.

With respect to the validation of conjugated saccharide (b) (4), based on results from the validation study, the conjugate saccharide assay has acceptable accuracy, specificity, linearity, precision, and robustness.

In validations of both saccharide and conjugate saccharide assays, some assay parameters were evaluated only for a subset of serotypes instead of all 15 serotypes. For example, robustness of the saccharide assay was evaluated for a (b) (4); repeatability of the conjugate saccharide assay was evaluated for a (b) (4); robustness of conjugate saccharide assay was evaluated for a (b) (4). Similarly, the laboratory equivalence of the saccharide assay was evaluated for a (b) (4). The product reviewer considers such a reduced validation strategy sufficient.

To conclude, I consider both saccharide and conjugate saccharide assays adequate for their intended uses.