



MEMORANDUM

To Administrative file for STN 125814

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Applicant Merck Sharp & Dohme LLC., a subsidiary of Merck & Co., Inc. (Merck)

Subject Review of analytical methods Pneumococcal 21-valent Conjugate Vaccine (V116)

Recommendation: Approval

Summary: Based on the validation and transfer data reviewed in this submission, the analytical methods for determination of polysaccharide Identity used for lot release testing of (b) (4) drug product (DP) are acceptable and are suitable for their intended purpose.

Background:

On October 19, 2023, Merck submitted a BLA for V116, 21-valent Pneumococcal Conjugate Vaccine (PCV) DP, for prevention of invasive disease and pneumonia caused by *Streptococcus pneumoniae* in individuals 18 years of age and older. The DP components are capsular polysaccharide from 21 serotypes (STs) 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and

35B that are individually conjugated to Cross-Reactive Material 197 (CRM197) carrier protein purified from *Corynebacterium diphtheriae* C7. The V116 DP is formulated in Polysorbate-20 (PS-20), and buffer containing 150 mM NaCl and 20 mM L- Histidine ((b) (4)). The V116 DP is formulated such that each 0.5 mL dose contains 4 µg of each of the 21 serotypes (STs) which are individually conjugated to approximately 65 µg of CRM197, 0.50 mg of PS-20, 1.55 mg of L-Histidine, and 4.49 mg of NaCl. The DP is filter sterile and filled into glass syringe barrel assembly stoppered with a plunger stopper to make a Pre Filled Syringes (PFS), stored at 2–8 °C. Each PFS has 0.5 mL dose of V116 ready for injection at intramuscular site.

The lot release tests for ((b) (4)) DP Identity (ID) are reviewed in this memo. These methods were previously reviewed for 15 valent Pneumococcal conjugated vaccine V114, from the same sponsor (STN125741, approved in July, 2021). The composition of V114 for 15 STs is- 1,3, 4,5,6A, 6B,7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, 33F conjugated to CRM197 containing same buffer composition as V116, but with alum adjuvant. The differences between the V116 and V114 formulations, other than the STs in the DP, are that V116 DP is formulated without adjuvant, at a lower PS-20 concentration, and at a higher target ST concentration. There are 6 common STs between V114 and V116 DPs-ST 3, 6A, 7F, 19A, 22F, 33F.

Documents Reviewed:

Section-3.2.S.4.2 - Analytical Procedures –ID

Section-3.2.S.4.3 and 3.2.R- Validation of Analytical Procedures –ID

Section-3.2.P.5.2 - Analytical Procedures – ID, saccharide content, conjugated saccharide content and ((b) (4)).

Section-3.2.P.5.3 and 3.2.R- Validation of Analytical Procedures – ID, saccharide content, conjugated saccharide content and ((b) (4)).

Section -3.2.R.- Method#A1986M19 (V4) or ATM1986M19 for ((b) (4)) Identity assay by ((b) (4)).

Section-3.2.R.8- Method# ATM-22859 for Saccharide assay and Identity for Pneumococcal (21V) conjugate Vaccine.

Section 3.2.P5.3.11- Validation of analytical procedures- Identity and Saccharide content.

Section- 3.2.R.8.23- AS-19-TT06-0017-MERV (V3)- Validation Report to addendum to the validation of the ((b) (4)) identification test for ((b) (4)) and Qualification of ((b) (4)) and Positive Controls for use in Method # A1986M19.

Section 3.2.P.5.3.11- Summary of validation of method for estimation of ID and saccharide content for V116 DP, at (b) (4) and transfer to MSD-(b) (4) and (b) (4) sites.

Section 3.2.R- Transfer Report# BVA-2023-Report-c1.0-MMD02870303- Report for transfer of method# ATM22859, "Saccharide Assay and Identity" from - (b) (4) to MSD, (b) (4) for testing of V116 DP.

Review

Methods Reviewed

1. Identity of (b) (4)
2. Identity of DP by (b) (4)

1. Methods for Identity for (b) (4) DP

The purpose of the methods are to confirm the identity of each 21 serotypes in (b) (4) and each component of the V116 (21 Valent). Test Method# A1986M19 (also referred to as ATM1986M19) is used for (b) (4) testing and Test Method# ATM22859, "Saccharide and Identity assay by (b) (4) method" is used in DP testing. The two methods for testing the identity of polysaccharides in (b) (4) DP are similar, therefore, both are discussed together in this section.

The identity and polysaccharide content methods were previously validated and approved for 15 valent (b) (4) for V114 DP (STN125741). A comparison of the matrix compositions between V114 and V116 DP manufacturing process steps demonstrates that the V114 and V116 (b) (4) matrices are equivalent, and therefore, are considered to be similar materials. Therefore, the same (b) (4) Identity method is used to confirm identity for Pneumococcal STs for both DPs (V114 and V116). In current submission, the sponsor submitted an addendum report (to previously validated V114 via study # AS-19-TT06-0017-MEVR) for Identity method for V116 (A1986M19) that encompasses both V114 and V116 serotypes.

Briefly, the test methods are (b) (4)



(b) (4)

The calculations, assay acceptance criteria and system suitability criteria (SSC) for (b) (4) DP Identity are listed below;

(b) (4)

For Identity testing of DP:

The DP sample ID of each ST, is confirmed by using the same data generated for DP potency (Saccharide content) if the following criteria are met:

(b) (4)

2. Review of Method validation for Identity for (b) (4) DP

(b) (4)

(b) (4)

(b) (4)

(b) (4)

2) Validation of method for DP Identity:

The Test Method# ATM22859- Identity and Saccharide by (b) (4) method is used for determination of identity and saccharide content in the DP V116 formulation for each of 21 STs components in DP. The test method for determination of Identity and Saccharide content for V114 DP was previously validated at (b) (4) and transferred to (b) (4) site in previous submission (STN125741).

In current submission, the sponsor provided documents to support the validation of the method at (b) (4) in accordance with ICH Q2(R1) and evaluated the accuracy, linearity, range, precision (repeatability and intermediate precision) and specificity, along with robustness of method. In this review, the identity part of the test method for DP is reviewed. The saccharide content method and validation is being reviewed by product office for this submission.

The method validation details at (b) (4)**Identity/ Specificity**

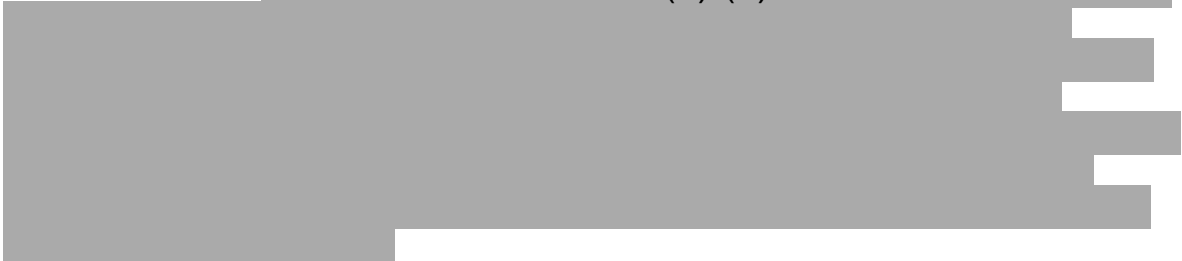
Identity was assessed using (b) (4)



The assessment of the method for determination of saccharide content for Linearity, precision, range, accuracy and robustness is being assessed by product office.

Transfer from (b) (4) to (b) (4)

The submission provides the data for transfer of the method from (b) (4) to MSD, (b) (4) and (b) (4) site as provided in Report# BVA-2023-Report-c1.0-MMD02870303. Method reproducibility (lab-to-lab) was established by evaluating intermediate precision and relative difference to demonstrate equivalency between (b) (4) and (b) (4). Representative DP samples were assessed for (b) (4) to qualify DP testing for all 21 serotypes in V116. The (b) (4) STs were selected because (b) (4)

**Conclusion**

The results from reproducibility studies for intermediate precision and equivalency demonstrated that the method is suitable for identity of V116 DP at (b) (4) site. The method is deemed qualified of performing the test for Identity by (b) (4) method# ATM-22859, in the DP V116 formulation. The transfer results confirm successful transfer of the method from (b) (4) to (b) (4) site.

Equivalency Assessment for V116 (b) (4)

An equivalency assessment was performed across the three laboratories to qualify the identity and saccharide content testing for V116 (b) (4). The equivalency assessment was performed to evaluate the difference between the sample results generated at each laboratory. (b) (4) generated a data set using the same DP batch, representative serotypes, and testing plan for the 100% dose level that were used for the transfer from (b) (4) to (b) (4). The data set generated at (b) (4) and (b) (4) site was compared to the data from (b) (4). Relative accuracy was assessed by calculating the percent difference and corresponding 90% confidence interval between each laboratory per serotype, . thus laboratory equivalency was confirmed between the three laboratories.

Conclusion

The identity assay # ATM22859 for testing of DP for 21 STs for V116 DP is suitable for its intended purpose at (b) (4). The saccharide method validation/transfer is being assessed by product office.