

Chemistry, Manufacturing, and Controls Statistical Review

Application Type	Original BLA
STN	125814/0
Applicant	Merck Sharp & Dohme, LLC
Established Name	Pneumococcal 21-valent Conjugate Vaccine
Trade Name	CAPVAXIVE
Indication	For active immunization for the prevention of invasive disease and pneumonia caused by Streptococcus pneumoniae serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B in adults 18 years of age and older.
Review Priority	Priority
CBER Received Date	10/18/2023
PDUFA Goal Date	06/17/2024
Product Office	OVRP
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EXECUTIVE SUMMARY

In this BLA, Merck seeks approval for CAPVAXIVE, a 21-valent pneumococcal conjugate vaccine. We were requested to conduct a CMC statistical review on the validation studies for total polysaccharide content and conjugated saccharide, the lab comparability assessments for those assays, and the (b) (4) validation for the polysaccharide powder (PnP) drug substance (DS) intermediates.

Merck provided validation reports for the drug product (DP) total polysaccharide content and conjugated saccharide content (b) (4) for all CAPVAXIE serotypes.

- The total polysaccharide content (b) (4) validation was completed at (b) (4). The validation results support the conclusion that the (b) (4) is suitably accurate, linear, and precise over an appropriate range when performed at (b) (4). Because this (b) (4) will be performed at (b) (4) other labs for commercial testing ((b) (4)), Merck completed transfer studies to demonstrate comparable performance to (b) (4) at each commercial lab. The transfer studies support a conclusion of similar performance at (b) (4). In addition, at CBER's request, Merck demonstrated that (b) (4) have similar performance to support using both labs for routine commercial testing.
- The DP conjugated saccharide content (b) (4) was validated at (b) (4), one of the commercial testing labs, and shown to have acceptable accuracy, linearity, and precision over an appropriate range. Because commercial testing will also be performed at (b) (4), Merck provided the results of a transfer study demonstrating comparability of the means and precision at (b) (4) and (b) (4).

Merck also provided the results of multiple validation studies to support use of the (b) (4) assay for testing the (b) (4). These validation studies were conducted to support licensure of other pneumococcal vaccines and were conducted with different instruments several decades ago. While the study designs and analyses used were not optimal, the results of my additional analyses suggest that the (b) (4) assay's performance will not increase the risk to the consumer.

In summary, I recommend approval of this original BLA.

REGULATORY BACKGROUND AND SOURCE OF INFORMATION

In this BLA, Merck seeks approval for CAPVAXIVE (referred to as V116 in the submission), a 21-valent pneumococcal conjugate vaccine. On 21 February 2024, the product reviewer requested us to conduct a CMC statistical review, focusing on the validation studies for total polysaccharide content and conjugated saccharide, the lab

comparability assessments for those assays, and the (b) (4) validation for the (b) (4) [REDACTED].

This review refers to the following files submitted to Module 3.2.R of BLA 125814/0:

- 56085-2021-Report-V4.0-MMD02342672
- (b) (4) Validation Report for Conjugated Saccharide Content (b) (4) for V116 Pneumoconjugate Vaccine
- BVA-2023-Report-v1.0-MMD02870303
- GQLMAS-2024-Report-v1.0-PRO-013729244
- BVA-2023-Report-v1.0-PRO-012941614
- BVA-2023-Report-v1.0-MMD02870303;

The documents about the (b) (4) assay in Module 3.2.S.4.2 of BLA 125814/0; and the responses (Modules 1.11) to the information requests (IR) sent on 2 May 2024 (BLA 125814/0.28) and 18 April 2024 (BLA 125814/0.26). The responses to the IRs were acceptable.

DISCUSSION OF PROTOCOLS, STUDIES OR ANALYSES, AND RESULTS

3.1 Drug Product Total Polysaccharide Content (b) (4) Validation

Total polysaccharide content testing is performed for release and during stability monitoring at Merck's (b) (4) sites for DP. Validation was performed at (b) (4) and a comparability study was performed to demonstrate acceptable performance at (b) (4).

3.1.1 Validation at (b) (4)

The validation study assessed the accuracy, precision (repeatability and intermediate precision), linearity, specificity, range, and robustness for all 21 serotypes in the vaccine.

Accuracy, linearity, and intermediate precision were assessed in one study. (b) (4)

[REDACTED]

[REDACTED]

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

(b) (4)

Reviewer's Comment: *While the comparability results support the conclusion of comparability between (b) (4), Merck only assessed comparability over a range of (b) (4) which is narrower than the range validated at (b) (4). However, since this range (b) (4) aligns with the DP specification, this is acceptable.*

(b) (4)

(b) (4)

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

Reviewer's Comment: *Merck did not assess comparability of the precision between [REDACTED]. However, the results from the individual comparability studies suggest that the two sites have similar precision.*

3.2 Drug Product Conjugated Saccharide Content [REDACTED] Validation

The DP conjugated saccharide content [REDACTED] is part of the DP release and stability testing and is performed at both [REDACTED] and [REDACTED] for commercial DP. Validation was completed at [REDACTED]. The validation study assessed the accuracy, precision (repeatability and intermediate precision), linearity, and range for all 21 serotypes. A comparability study was used to validate [REDACTED] and establish comparability of the two commercial testing sites.

3.2.1 Validation at [REDACTED]

Accuracy, linearity, and intermediate precision were measured in a single study using

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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

(b) (4)

CONCLUSIONS

Merck provided the validation reports for DP total polysaccharide content and conjugated saccharide content (b) (4) for all CAPVAXIE serotypes. The total polysaccharide content (b) (4) validation was completed at (b) (4). The validation results support the conclusion that the assay is suitably accurate, linear, and precise over an appropriate range (b) (4) when performed at (b) (4). Because this (b) (4) will be performed at two other labs for commercial testing ((b) (4)), Merck completed transfer studies to demonstrate comparable performance at each commercial lab. The transfer studies for (b) (4) support a conclusion of similar performance at those two labs. In addition, at CBER's request, Merck demonstrated that (b) (4) have similar performance.

The DP conjugated saccharide content (b) (4) was validated at (b) (4), one of the commercial testing labs, and shown to have acceptable accuracy, linearity, and precision over an appropriate range. Because commercial testing will also be performed at (b) (4), Merck provided the results of a transfer study demonstrating comparability of the means and precision at (b) (4).

Merck also provided the results of multiple validation studies to support use of the (b) (4) assay for testing the (b) (4). These validation studies were conducted to support licensure of other pneumococcal vaccines and were conducted with different instruments several decades ago. While the study designs and analyses used were not optimal, the results of additional analyses I conducted suggest that the (b) (4) assay's performance will not increase the risk to the consumer.

Overall, I recommend approval of this original BLA.