



DBSQC/OCBQ ANALYTICAL METHOD REVIEW MEMO

To: The file STN 125741/0

From: Claire H. Wernly, Ph.D.

Reviewer	Role	Date finalized	Stamp	Supervisor	Stamp
Claire H. Wernly, Ph.D.	Lead Reviewer	07/08/2021		James L. Kenney, D.Sc.	
Emnet Yitbarek, Ph.D.	Reviewer	05/06/2021		Kori Francis	
M. Nahid Parvin, Ph.D.	Reviewer	06/30/2021		Muhammad Shahabuddin, Ph.D.	

Through Maryna Eichelberger Ph.D.
Division Director, DBSQC

Applicant: Merck Sharp and Dohme Corp.

Subject: Review of Analytical Methods used for Pneumococcal 15-Valent Conjugate Vaccine (CRM197 Protein), (b) (4) (V114), Drug Substance (DS), Drug Product (DP) and Lot Release

Recommendation: Approval

Summary:

The following analytical methods used for lot release of V114 and the associated analytic method validations or qualifications, were reviewed:

1. (b) (4) (Claire Wernly)
2. Endotoxin for (b) (4) DP (Claire Wernly)
3. Sterility for DP (Claire Wernly)
4. Appearance of (b) (4) DP by Opalescence (Emnet Yitbarek)
5. Determination of Aluminum in DP by (b) (4) (Emnet Yitbarek)
6. (b) (4) (Emnet Yitbarek)
7. (b) (4) for DP (Emnet Yitbarek)

8. Polysorbate-20 (PS-20) content in DP by (b) (4) (Emnet Yitbarek)
9. Determination of Identity and Total polysaccharide content in drug product by (b) (4) (M. Nahid Parvin)
10. Determination of Conjugated Saccharide content by (b) (4) (M. Nahid Parvin)

Conclusion: The analytical methods and their validations and/or qualifications reviewed for the Pneumococcal 15-Valent Conjugate Vaccine (b) (4) drug product were found to be adequate for their intended use.

Documents Reviewed:

Information in sections of the original submission that describe control of DS and DP (3.2.S.4 and 3.2.P.5, respectively), including descriptions of DS and DP specifications, analytical procedures of DS and DP and validation of these analytical procedures were reviewed. Additional information in amendments specified by each reviewer were also reviewed.

Background:

On 21 October, 2020, Merck submitted this BLA for Pneumococcal 15-Valent Conjugate Vaccine [CRM197 Protein], (b) (4) (V114). V114 is indicated for active immunization for the prevention of invasive pneumococcal disease caused by *Streptococcus pneumoniae* 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.

V114 contains the capsular pneumococcal polysaccharides (PnPs) present in Prevnar13® (STN 125324) (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) and two new additional serotypes (22F, and 33F), individually linked to non-toxic diphtheria cross reactive carrier 197 protein (CRM₁₉₇) from *Corynebacterium diphtheriae* C7. Due to differences in chemical structure and properties, serotypes 1, 3, 4, 5, 9V, 14, 22F and 33F (b) (4) 6A, 6B, 7F, 18C, 19A, 19F and 23F (b) (4) . Each conjugate is a distinct DS referred to as a serotype-specific monovalent bulk conjugate (MBC). The 15 serotype-specific MBCs are combined (b) (4) of the final DP.

V114 final DP is a sterile liquid suspension for intramuscular injection, supplied in a 0.5 mL single-dose pre-filled syringe. Each dose contains 2.0 µg of polysaccharide serotypes (1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F) and 4.0 µg of polysaccharide serotype 6B, 30 µg of CRM₁₉₇ carrier protein, (b) (4) L-histidine, 1 mg of polysorbate 20, (b) (4) sodium chloride, water for injection and 125 µg of aluminum phosphate adjuvant.

The DBSQC reviews BLAs and their supplements to ensure analytical methods are appropriate, properly validated and the test methods are suitable for their intended use. These review activities support DBSQC's lot-release mission, which is the

confirmatory testing of submitted product samples and review of manufacturers' lot-release protocols to ensure biological products are released per their product's licensed test method specifications. Therefore, this review will focus on the qualifications of analytical testing methods and their validation for testing DS MBC serotypes and the final V114 DP to ensure these methods are suitable under their actual conditions of use.

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

(b) (4)

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2. Endotoxin, Claire Wernly

Introduction

The test is performed on (b) (4)
on V114 DP at (b) (4)

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(b) (4)

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(b) (4)

(b) (4) Bacterial Endotoxin (b) (4) Method for DP:

Merck qualified (b) (4) for testing the V114 DP. CBER asked Merck to specify (b) (4) method; and Merck stated their primary method for endotoxin determination for V114 DP is the (b) (4) method.

(b) (4)

(b) (4)

(b) (4)

Information Requests and Reviews

The following IR was submitted to the Sponsor on April 16, 2021, with response received in Amendment #29 on April 23, 2021:

Bacterial endotoxin test is performed for (b) (4) drug product. The method verification result summaries reported in 3.2.S.4.3 for (b) (4) 3.2.P.5.3 for DP are not complete. Please provide complete bacterial endotoxin qualification reports for (b) (4) DP to show the method is suitable for its intended use. Please include maximum valid (b) (4), lot numbers tested, the final selected testing

(b) (4) and endotoxin test results for each lot tested. For DP, please clarify which method will be the primary method used for testing, as a summary of results was presented for (b) (4)

Review of the Response

The Sponsor responded by providing detailed qualification reports. In addition, the Sponsor indicated that for V114 DP, their primary method for endotoxin determination is the (b) (4) method and the (b) (4) method will be their (b) (4) method (IR response – Amendment 125741/0/29). The information provided is acceptable.

Conclusion

Merck submitted bacterial endotoxin concentration results of several lots of (b) (4) V114 DP and all were found to be within their proposed release specification of (b) (4). After review of the (b) (4) test for (b) (4) V114 DP, this reviewer concludes the test methods were performed and compliant with (b) (4)

3. Sterility, Claire Wernly

Introduction

This test is performed on V114 DP at (b) (4)

Review of Method:

Merck performed sterility testing using the (b) (4)

Sterility Test Qualification for DP:

(b) (4)

(b) (4)



Information Requests and Reviews

The following IR was submitted to the Sponsor on April 16, 2021, with response received in Amendment #29 on April 23, 2021:

(b) (4)



Review of the Response

The Sponsor responded by providing a detailed qualification report. The information provided is acceptable.

(b) (4)



Conclusion

After a thorough review of the information submitted in this BLA, this reviewer finds Merck's bioburden, sterility, and endotoxin test method qualifications were acceptable and provide evidence of method suitability under the actual conditions of use. Therefore, this reviewer finds these methods acceptable for their intended purpose and recommends their approval.

4. Appearance of (b) (4) DP by Opalescence (Emnet Yitbarek)

Appearance is a (b) (4)

[Redacted]

The specifications for appearance of (b) (4) DP release are as follows:

- o (b) (4)
- o DP: Opalescent (b) (4)

(b) (4)

[Redacted]

Method Verification for DP

Verification of the appearance method was conducted using (b) (4) Drug Product (DP) samples (b) (4)

[Redacted]

Conclusion: The opalescence method is adequately described and verified for determining appearance of V114 DP (b) (4) samples.

(b) (4)

[Redacted]

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(b) (4)

7. Aluminum Content by (b) (4)

for DP (Emnet Yitbarek)

The aluminum (Al) concentration (mg/mL) in VAXNEUVANCE DP samples is determined by (b) (4). The DP is a suspension containing aluminum phosphate adjuvant (APA). The technique is based on (b) (4)

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

(b) (4)

Conclusion: The (b) (4) method is adequately described and validated for determining AI in V114 DP samples.

8. Polysorbate-20 (PS-20) content by (b) (4) for DP (Emnet Yitbarek)

The PS-20 concentration (b) (4) in VAXNEUVANCE DP samples is determined by (b) (4)

[Redacted]

- (b) (4)
- | [Redacted]

(b) (4) [redacted]

- | [redacted]
- | [redacted]
- | [redacted]
- | [redacted]

[redacted]

Information Request:

IR from 02/01/21:

We are reviewing your BLA (STN 125741), received on November 17, 2020 for VAXNEUVANCE, a Pneumococcal 15-valent Conjugate Vaccine, and have the following requests for additional information:

For validation of the Polysorbate-20 (PS-20) content by (b) (4) [redacted]

IR from 02/17/21:

This pertains to your February 10, 2021 response to our Information Request #3, dated February 1, 2021, regarding validation of the Polysorbate-20 (PS-20) content by (b) (4) [redacted] method:

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

(b) (4)



Conclusion: The (b) (4) method is adequately described and validated for determining PS-20 in V114 DP samples.

9. Determination of Identity and Total polysaccharide content in drug product by (b) (4) (M. Nahid Parvin)

9.1 Method:

The analytical method explained in Section 3.2.P.5.2. is a (b) (4)



(b) (4)



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

Identity of each serotype in the product is confirmed (b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

The method is used for testing Identity and potency of V114 drug product. Lot release testing will be performed at the (b) (4) quality control facility using SOP A4148M06 which is equivalent to SOP AP919.4136 at the (b) (4) site.

9.2 Validation of method to determine Total Saccharide content by (b) (4)

Method validation was performed according to a method validation protocol and is documented in method validation report 56085-2016-TR-0071PD at (b) (4)

[Redacted]

(b) (4)

[Redacted]

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(b) (4)



9.3 Validation of method to determine DP Identity by (b) (4)

(b) (4)





The above test results met the identity criteria which demonstrates the validation of the identity assay.

9.4 Qualification of (b) (4) for the total saccharide content to (b) (4) site

The Total Polysaccharide (Ps) (b) (4) was validated for V114 Drug Product at (b) (4) using all 15 serotypes as described above. The analytical (b) (4) and qualification of

this assay (b) (4) QC laboratory at (b) (4) was carried out per qualification protocol AS-17-TT24-0005-QP Rev 1.0 and is documented in qualification report AS-17-TT24-0008-QR Rev 1.0.

(b) (4)

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(b) (4)

[Redacted]

[Redacted]

[Redacted]

**10. Determination of Conjugated Saccharide content by (b) (4)
(M. Nahid Parvin)**

10.1 Method:

The analytical method explained in Section 3.2.P.5.2. is (b) (4)

[Redacted]

[Redacted]

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

(b) (4)



10.3 CBER Information Requests and Reviews:

The following information request was submitted to the sponsor on March 5, 2021. The response was received on March 12, 2021.

CBER IR-1:

Information request for STN 125741/0 Pneumococcal 15-valent Conjugate Vaccine [CRM197 Protein], (b) (4) (V114) original BLA for following Analytical Procedures and method validations:

A. Identity and Total Saccharide content by (b) (4):

- 1) Please provide a copy of current SOP (A4148M06 / AP919.4136) for Identity and Saccharide content by (b) (4)
- 2) Robustness report is not included in the validation report 56085-2016-TR-0071PD. Please provide the robustness report.

B. (b) (4) :

- 1) Please provide a copy of current SOP (A4148M14 / AP919.4151) for CRM Conjugated Saccharide content by (b) (4).
- 2) Robustness report is not included in the validation report AS-18-TT26-0007-MEVR. Please provide the robustness report.
- 3) Please provide a copy of current validation protocol AS-18-TT26-0006-MEVP for the (b) (4) .

Sponsor Response:

Sponsor provided all the requested information.

Reviewer Response:

The information was reviewed and relevant information is included in the method descriptions and validations above. The Sponsor's response is acceptable.

The following information request was submitted to the sponsor on April 16, 2021. The response was received on April 23, 2021.

CBER IR-2:

- 1) It is unclear if you are planning to perform the (b) (4) for release testing at the (b) (4) site. If you do plan to use this assay in (b) (4), please provide a qualification report for the assay at (b) (4) that includes relative accuracy, intermediate precision, and comparability of results obtained at this site and the site at (b) (4) where the assay was validated. Please respond by 04/30/2021.

Sponsor Response:

The Conjugated Saccharide Content by (b) (4) method (b) (4) was developed and qualified by (b) (4) at the (b) (4) site for characterization of clinical lots. The method was then validated at the commercial laboratory at (b) (4). This is the (b) (4) laboratory currently supporting commercial release and stability testing for V114 DP with this method.

Reviewer Response:

Sponsor's response is acceptable.

The following information request was submitted to the sponsor on June 04, 2021. The response was received on June 10, 2021.

CBER IR-3:

Please address the following regarding Total Saccharide Content and Conjugated Saccharide Content (b) (4) analytical procedures and method validations:

1) You are using (b) (4) reference standard for qualification and/or stability studies of the (b) (4) reference standards. Along with other parameters you describe, we recommend that you include a measure of (b) (4) performance, e.g., (b) (4) measurements of standards (b) (4) are tested, as qualification acceptance criteria and for tracking stability.

2) You have validated the (b) (4) to read and calculate the reportable results for these (b) (4). Please provide the (b) (4) templates for Saccharide Content and Conjugated Saccharide Content (b) (4) so that concurrent lot release testing at CBER aligns with the tests performed in your laboratory. In addition, please provide the results of the following system suitability criteria and test acceptance criteria for at least (b) (4) lots for each serotype: (b) (4)

Sponsor Response and Commitment:

1) The Applicant agreed with the importance of monitoring reference standard performance in the assay and is in the process of establishing an (b) (4) assay monitoring program for V114 reference standards. Once established, reference

standard data, including relevant system suitability attributes, will be tracked and trended. Due to method platform similarity and the (b) (4) standards in both the Saccharide Content and Conjugated Saccharide Content (b) (4), the applicant has selected the Saccharide Content method as the (b) (4) used for monitoring reference standard performance. Until the (b) (4) monitoring program is established, control of the reference standards is assured via (b) (4) testing which mitigates risk of performance drift.

The applicant committed to provide an interim update on the establishment of (b) (4) Data Monitoring to further enable stability tracking of reference standard performance by end of Q3 2021. Note that in advance of the assay monitoring program being fully established, the reference standard performance is assured via the data collection described in response # 2 and the commitment to provide the agency with system suitability data for the next (b) (4) commercial batches (which will extend beyond Q3 2021).

2) The (b) (4) is used for the Saccharide Content and Conjugated Saccharide Content (b) (4). A PDF version of the current template “CRM(b) (4) _Total_Ps_V114_DP_(b) (4)_Rev7.0.pdf” is provided. The (b) (4) is under revision to update the (b) (4) selection limits for the Conjugated Saccharide Content method. The change to the (b) (4) selection limits does not affect the (b) (4) which are selected; but ensures that the correct number of validated (b) (4) are selected. There is no change to the Saccharide Content method; the (b) (4) which is used for (b) (4) methods will be updated to reflect the revised limits for Conjugated Saccharide method only. There is no impact to any (b) (4) data generated to date.

Applicant would like to engage with the agency so that lot release testing at CBER aligns with the applicant’s testing. The sponsor is willing to provide applicant-specific reagents and additional (b) (4), and an updated (b) (4) once finalized. The sponsor explained that system suitability criteria and test acceptance criteria are not yet available for (b) (4) lots for each serotype, as requested but do provide information using fewer lots: Saccharide Content for (b) (4) Lots (Lot# (b) (4), and Lot#(b) (4)) and Conjugated Saccharide for (b) (4) Lots (Lot# (b) (4)). The (b) (4) used at the commercial testing site was submitted as an attachment titled “V114 DP (b) (4) FDA IR No. 26 System Suitability Data.xls”.

The applicant committed to providing the same system suitability criteria and test acceptance criteria for Saccharide Content and Conjugated Saccharide Content (b) (4) for the next (b) (4) commercial scale batches as a single update.

Reviewer Response:

Sponsor's response is acceptable. They have been instructed to submit this information as noted in the comments below. We have not asked for any reagents or samples at this time because of the restriction of limited laboratory activities at CBER due to Covid-19 pandemic. We will request the critical reagents and samples when lot release testing resumes at CBER.

The CBER comments were communicated to the sponsor on June 24, 2021. The sponsor's response was received on June 28, 2021.

CBER Comments:

- 1) You have committed to provide an interim update of the establishment of an (b) (4) Data Monitoring program to further enable stability tracking of reference standard performance by end of Q3 2021. Please submit this information to STN 125741 when available for our review.
- 2) You have committed to provide the system suitability criteria and test acceptance criteria for Saccharide Content and Conjugated Saccharide Content (b) (4) that include analysis of data from the next (b) (4) commercial scale batches. Please submit these data as a product correspondence to STN 125741.
- 3) We will request critical reagents and the spreadsheet to perform and analyze the data for (b) (4) assays when lot release testing resumes at CBER. Please provide the contact person's name and email address for future correspondence regarding the (b) (4) assays for lot release purposes.

Sponsor's Response:

- 1) The Applicant acknowledged the Agency's request to submit the previously committed interim update of the establishment of an (b) (4) Data Monitoring program by the end of Q3 2021 to STN 125741.
- 2) The Applicant acknowledged the Agency's request to submit the previously committed system suitability criteria and test acceptance criteria for Saccharide Content and Conjugated Saccharide Content (b) (4) that include analysis of data from the next (b) (4) commercial scale batches as a product correspondence to STN 125741.
- 3) The contact for future correspondence regarding the (b) (4) assays for lot release purposes is as follows:

Victoria Towne

Director, Biologics and Vaccines Analytics

victoria_towne@merck.com

and

Aileen Ryan

Associate Director, Quality Laboratories Operations

aileen.ryan@merck.com

Reviewer Response:

Sponsor's response is acceptable.

Conclusion: The assay to determine conjugated saccharide content by (b) (4) [REDACTED] is adequately described. The data submitted for review, demonstrate specificity, precision, linearity/relative accuracy, range and robustness of the (b) (4) and is suitable for its intended use.