DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

DBSQC/OCBQ ANALYTICAL METHOD REVIEW MEMO

To: The file STN 125701

From:

Reviewer	Role	Date finalized	Stamp	Supervisor	Stamp
Anil Choudhary	Lead Reviewer	10/22/2019		Dr. Muhammad Shahabuddin	
Hsiaoling Wang Tao Pan	Reviewer	03/05/2020		Francis Kori	
Hyesuk Kong	Reviewer	03/10/2020		Dr. James L. Kenney	

Through: Maryna Eichelberger PhD., Division Director, DBSQC

Applicant: Sanofi Pasteur

Proprietary Name: MenQuadfi™
Proper Name: Meningococcal (Groups A, C, Y, W) Conjugate Vaccine

Subject: Review of CMC Analytical Methods used for Lot Release of MenQuadfi™ Drug Substance and Drug Product

---

Recommendation: Approval.
Tao Pan and Hsiaoling Wang reviewed methods # 1 to 14, Anil Choudhary reviewed method #15, Hyesuk Kong reviewed methods # 16 to 18 as listed below.

Summary:
The following analytical methods used for lot release of MenQuadfi™ (b) (4) Drug Product (DP) and the associated analytic method validations or qualifications, were reviewed:

Methods #1 to 14 were reviewed by Hsiaoling Wang and Tao Pan
1. Protein Content by (b) (4) ((b) (4) DP)
2. (b) (4)
3. (b) (4)
4. (b) (4)
5. (b) (4)
6. (b) (4)
7. (b) (4)
8. (b) (4)
9. (b) (4)

10. (b) (4)
11. Total & Free Polysaccharide Quantitation of MenQuad-TT Conjugate Vaccine by (b) (4) (DP)
12. Volume Check (DP)
13. Physical Appearance: Major A & Major B (DP)
14. (b) (4)
15. Identity (DP): Anil Choudhary
16. Bioburden (b) (4): Hyesuk Kong
17. Sterility (DP): Hyesuk Kong
18. Endotoxin ((b) (4) DP): Hyesuk Kong

Conclusion: The analytical methods and their validations and/or qualifications reviewed for the MenQuadfi™ drug substance and drug product were found to be adequate for their intended use. Except (b) (4) assay that was performed and validated by (b) (4), all the other methods are performed and validated at the Swiftwater site of Sanofi Pasteur, Inc.

Sections Reviewed

The following sections of STN125701 were reviewed: Initial submission, primarily sections describing DS and DP analytical procedures, assay validations, responses to information requests (the date of each response is inserted in the text);

1. Section 3.2.S.4.2. Analytical Procedures (Drug Substance)
2. Section 3.2.S.4.3. Validation of Analytical Procedures (Drug Substance)
3. Section Batch Analyses
4. Section Specification of Drug Product
5. Section 3.3.P.5.2. Analytical Procedures (Drug Product)
6. Section 3.2.P.5.3. Validation of Analytical Procedures (Drug Product)
7. Section Batch Analyses
8. Amendment 14, dated November 14, 2019: Section 1.11.1 Quality Information Amendment: Determination of Volume in Final Containers (Doc # Q_0277969)
9. Amendment 21, dated Jan. 17, 2020: Section 1.11.1 Quality Information Amendment
10. Amendment 22, dated Jan. 31, 2020: Section 1.11.1 Quality Information Amendment: SWT-REP-021698 for Bioburden Validation Report.
11. Protocols of additional validation study, submitted Jan. 27, 2020 through email for Supplemental Validation for Total Protein by (b) (4), Total Polysaccharide ,(b) (4) , Free Polysaccharide for Menquadfi (b) (4) .
12. Amendment 23, dated Feb. 10, 2020: SWT-REP_021709: Validation of Analytical Procedures - (b) (4)

13. Amendment 24, dated Feb. 12, 2020: Section 3.2.S.4.3. Validation of Analytical Procedures SWT-REP-021752. Supplemental Validation Report for MenQuad-TT Total Polysaccharide by (b) (4) Method SWT-SWI-003399.
14. Amendment 25, dated Feb. 14, 2020: Section 1.11.1 Quality Information Amendment
15. Amendment 26, dated Feb. 24, 2020: Section 3.2.S.4.3. Validation of Analytical Procedures.

Background:

On 26 April, 2019, Sanofi submitted this BLA for approval for MenQuadfi™. It is indicated for active primary and booster immunization for the prevention of invasive meningococcal disease caused by *Neisseria meningitidis* Serogroups A, C, Y, and W in individuals 2 years of age and older.

The MenQuadfi™ DP is manufactured by formulating four DS serogroup-specific polysaccharide antigens purified from *Neisseria meningitidis* Serogroups A, C, Y, and W, each separately conjugated to Tetanus Toxoid Protein. The MenQuadfi™ DP is a sterile solution containing sodium acetate and sodium chloride buffers for intramuscular injection. It is supplied in 0.5 mL single-dose vials.

DBSQC reviews BLAs and their supplements to ensure analytical methods are appropriately validated and suitable for the intended purpose. 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.

Review

1. Protein Content by (b) (4) (Hsiaoling Wang and Tao Pan)

The proposed specifications for (b) (4) of all four serogroup conjugates are (b) (4) . The proposed specification for DP is (b) (4) µg/mL

Method
(b) (4)

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

(b) (4)

For Drug Product:

The method was validated using (b) (4) of DP sample and results are summarized in the Table 1.

Table 1. Summary of Validation Results for Protein Content in DP

Validation Characteristics	Acceptance Criteria	Results
Specificity	(b) (4)	
Accuracy		
Repeatability		
Intermediate precision		
Linearity		
Range		
LOQ		
Robustness		

(b) (4)

First Information Request and Review

The following IRs were sent to the sponsor on Oct. 29, 2019 and the responses were received on Nov. 14, 2019 in amendment 14 regarding the method and its validation:

a. Please explain the (b) (4) acceptance criterion of (b) (4) for the control of (b) (4) in SOP of "Protein Content by (b) (4)" (Q_0578617).

(b) (4)

iii. (b) (4)

c. Regarding the validation report “Validation of Instruction Q_0278048, "(b) (4) Protein Assay" for Application to the MenQuad-TT Drug Product” (Q_0604074):
The accuracy study does not demonstrate assay suitability for the intended purpose because it does not evaluate the impact of sample matrix on assay performance. Please provide appropriate spike-recovery data to demonstrate assay suitability for measuring protein concentration of Drug Product.

Second Information Request and Review

The requested spike-recovery data was not provided. The accuracy was not evaluated. A follow-up IR was sent to the sponsor on Dec. 14, 2019. The responses were received on Jan. 17, 2020 after a brief tele-conference on Jan. 14, 2020 requested bt the sponsor, with final responses received on February 24, 2020.

(b) (4)

Review of the response (#a)

The sponsor agreed to perform the supplemental validation study for the assay in the response received on January 14, 2020, and the supplement validation report (SWT-REP-021767) was received on February 24, 2020 in amendment 26.

(b) (4)

For the accuracy of the DP, DP samples (b) (4) the acceptance criterion, recovery between (b) (4), was met; and the accuracy of the assay for DP was validated for the range of (b) (4).

For specificity, (b) (4) samples of four serotypes with (b) (4) protein concentrations (b) (4) The acceptance criterion, Bias% (b) (4), was met; and the specificity of the assay was demonstrated at both the low and high end of the range for (b) (4), and in turn for DP.

Based on the accuracy and specificity validation, the range of the assay can be defined as (b) (4), and LOQ is verified as (b) (4). The response from the sponsor in amendment 26 is acceptable.

Conclusion

Based on the information provided by original submission and subsequent amendments, this method was adequately validated for the intended use.

(b) (4)

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

(b) (4)

(b) (4)

4. (b) (4) **determination by** (b) (4) **(Hsiaoling Wang and Tao Pan)**
The proposed specifications for (b) (4) of all (b) (4) DP are more than (b) (4) .

Method
(b) (4)

Method Validation

(b) (4)

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

First Information Request and Review

The following IRs regarding the method and its validation were sent to the sponsor on Oct. 29, 2019 and the responses were received on Nov. 14, 2019 in amendment 14.

a. Regarding the analytical procedure (b) (4) [redacted]" (Q_0578199):

(b) (4) [redacted]

19 pages have been determined to be not releasabe: (b)(4)

(b) (4)

11. Total and Free Polysaccharide Quantitation of MenQuad-TT Conjugate Vaccine by (b) (4) **(Hsiaoling Wang and Tao Pan)**

The proposed specifications for polysaccharide contents of all four serogroup conjugates are (b) (4) . The proposed specifications for free polysaccharide are (b) (4) for all four serogroup conjugates.

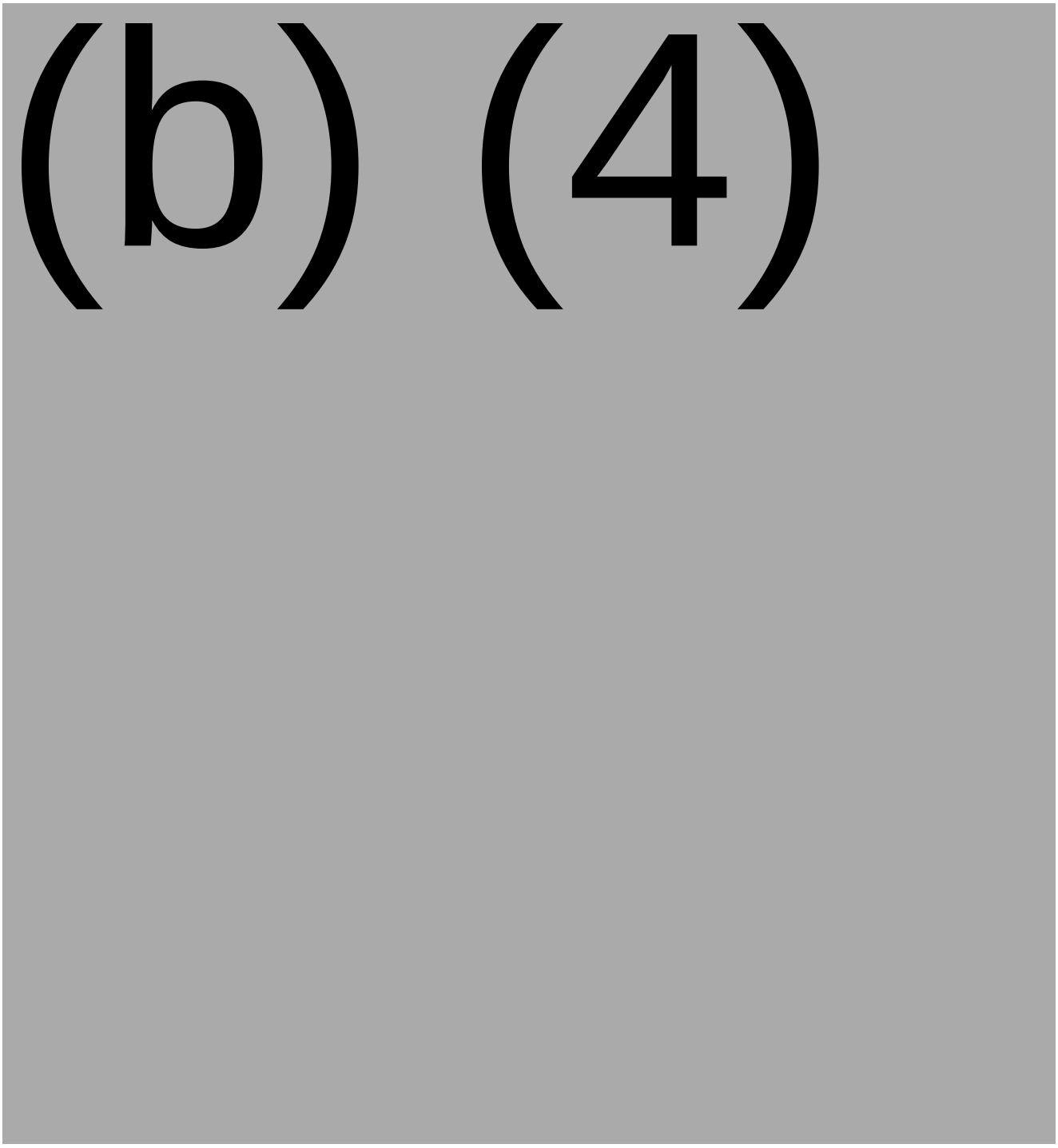
Method

The assay procedures for total and free polysaccharide (PS) are described in document Q_0578298. (b) (4)

(b) (4)

(b) (4)

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



Information Request and Review

The following IRs were sent to the sponsor on Oct. 29, 2019 and the responses were received on Nov. 14, 2019 in amendment 14 regarding the method and its validation.

> Regarding the validation report “Report for Protocol Q_0633361, Validation Extension of Q_0279993 Total & Free Polysaccharide Quantitation of MenQuad-

TT Conjugate Vaccine to include (b) (4) " (Q_0635191) (for serogroups A, W and Y):

i. Please provide the methods used to determine concentration of activated polysaccharide standards in Table 3. Please provide data to demonstrate the total and free polysaccharide quantity measurements are not impacted by the sample matrix.
ii. Please provide the methods used for the concentration determination of (b) (4) in Table 4 and submit data to demonstrate assay results are not impacted by the sample matrix.

Review of the Response:

i. In the response, the sponsor indicated the activated polysaccharide standard for serogroup A was determined by an orthogonal method Q_0580864 and the activated polysaccharide standards for serogroups C, W and Y was determined by an orthogonal method Q_0277590. Specificity and accuracy studies of these activated polysaccharide standard were demonstrated in validation reports Q_0265220 and Q_0264795, respectively. The response is acceptable.
ii. In the response, the sponsor stated that the concentration for serogroup A conjugate was determined by an orthogonal method Q_0580864 and the concentration for serogroups C, W and Y was determined by an orthogonal method Q_0277590. Specificity and accuracy studies of conjugate C and conjugates of A, W and Y were demonstrated in validation reports Q_0265220 and Q_0264795, respectively. The response is acceptable.

Conclusion
The method is adequately described and validated for the intended use.

12. Determination of Volume in Final Containers (Hsiaoling Wang and Tao Pan)

The specification for DP in final container is NLT 0.5 mL/vial.

Method
The volume check procedures are described in section 3.2.P.5.2. and document Q_0277976, which is performed in compliance with (b) (4)

Method Validation
This compendial method does not require validation. The analysts were qualified to perform the test after appropriate trainings.

Information Request and Review
The following IRs were sent to the sponsor on Oct. 29, 2019 and the responses were received on Nov. 14, 2019 in amendment 14 regarding the method and its validation.

Please add a (b) (4) value for Menquadifi DP sample in appendix 4 of the analytical procedure of "Determination of Volume in Final Containers" (Q_0277976).

Review of the response
The (b) (4) of (b) (4) for the DP sample was added to the updated analytical procedures. The response is satisfactory.

Conclusion
The procedure is suitable for its intended use.

13. Physical Appearance: Major A and major B (Hsiaoling Wang and Tao Pan)

Major A test for physical appearance is an inspection of clarity, which determines that the product is free from extraneous color, undissolved or particulate matter. The specifications for Major A are: major defects (b) (4), minor defects (b) (4) and critical defect=(b)(.

Major B test for physical appearance is an inspection of (b) (4), The latter is noting any (b) (4). The specifications for major B are: rejects of (b) (4); and rejects of (b) (4).

Method
The Major A procedures are described in section 3.2.P.5.2. During the 100% visual product inspection, DP vial appearance is compared with the product description, which is in compliance with the requirements set forth in the foreign and particulate matter section of (b) (4). The visual inspection workstation utilized for inspection is in compliance with (b) (4).

The Major B procedures are described in section 3.2.P.5.2. The DP vial is examined against a (b) (4) to confirm that the solution remains (b) (4), exhibiting no non-characteristic (b) (4). The vial product is also tested for (b) (4).

Method Validation
Visual inspection of DP does not require validation. Test quality is based on the appropriate training of the analysts prior to performing the visual inspection.

Conclusion
The procedure is suitable for its intended use.

14. (b) (4) Determination (Hsiaoling Wang and Tao Pan)

The specification for DP is (b) (4).

Method
(b) (4)

Conclusion
The procedure is suitable for its intended use.

15. Identity Test (Anil Choudhary)

Method

The SOP- Q 0578457 describes the (b) (4) method for identification of meningococcal polysaccharides (serogroups A, C, Y and W135) and carrier protein (tetanus toxoid) by (b) (4) tetravalent, conjugated and unconjugated, *N. meningitidis* Polysaccharide Tetanus Toxoid Conjugate formulations of MenQUAD-TT. (b) (4)

Method Validation

The validation of the assay method-SOP Q 0578457, was performed in conformance with ICH Q2(R1) guidelines, for establishing the “Identity” of the meningococcal polysaccharides (serogroups A, C, Y and W135) and
carrier protein (tetanus toxoid). The ICH guidelines require the assessment of the specificity parameter only for validation of a method used for ID of drug substance/ product.
In the ID validation document submitted by sponsor (Document# C017334), specificity was assessed along with the intermediate precision of the assay method# Q 0578457.

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

(b) (4)

All results met the acceptance criteria for positive or negative samples for specificity and 100% identification for intermediate precision in (b) (4) runs.

Assay robustness was completed during development of the assay. The robustness studies evaluated such parameters as (b) (4) . No significant impact was reported to assay performance during robustness testing. Assay was concluded to be robust for all parameters tested.

Conclusion
The method SOP Q 0578457 was validated for demonstrating the Identity and intermediate precision of the meningococcal polysaccharides (serogroups A, C, Y and W135) and carrier protein (tetanus toxoid) drug components. The specificity and intermediate precision parameters were evaluated and all the specifications were met satisfactorily. The sponsor provided the reference numbers for the documents that included evaluation of the robustness of the assay in the reference section of the validation document. As per ICH Q2R1 guidelines, the specificity is the only parameter needed to demonstrate the identity, for an assay and therefore I did not request the additional data for review of assay robustness. The method is suitable for the intended purpose of demonstrating the identity of meningococcal polysaccharides (serogroups A, C, Y and W135) and carrier protein (tetanus toxoid) in MenQuadfi and the results are acceptable to DBSQC. The assay method is approvable.

16. Microbial Bioburden Test Method (Hyesuk Kong)

Method
Bioburden testing, or total viable count testing, is the measure of microbial contamination/burden levels on or in a product. Bioburden can be introduced from the raw materials used in the manufacturing process or be introduced via the workforce or manufacturing environment. The (b) (4) bioburden test is used for (b) (4) products in accordance with (b) (4) to detect microorganisms to assure the bioburden load is below specification. Bioburden tests are typically performed in the manufacturing process prior to sterility filtration to ensure bioburden load does not overwhelm filtration capacity. Test samples are (b) (4)

(b) (4)

Bioburden Information Request and Review

The following Information Request (IR) was submitted to the Sponsor on 6 November 2019 and the response was received on 31 January 2020 in amendment 125701/0/22.

In your November 21, 2019, response to dated 06 November, 2019, it was stated that "based on acceptable (b) (4)

(b) (4) *is acceptable". CBER finds this response to be unacceptable, as faster growing burden can mask the detection of* (b) (4) *in your alternate method, information that is important for production process quality control.*

Please perform your method in accordance with (b) (4) *and complete the qualification by testing* (b) (4) *or provide a complete validation of your bioburden method in accordance with* (b) (4) *demonstrating your alternate method will provide assurances of its effectiveness using your product matrix that is equal to or greater than the assurances provided by the* (b) (4) *method. CBER expects this validation to include known environmental* (b) (4) *isolates from your facility in the limit of detection study, so an adequate comparison can be demonstrated in accordance with CFR 610.9(a).*

Review of the Response
Sponsor submitted a bioburden qualification report performed using (b) (4) on (b) (4) media for (b) (4) and one environmental isolate ((b) (4)). This reviewer found all requested information in the report. The response is acceptable.

17. Sterility Test (Hyesuk Kong)

Method
The (b) (4) sterility test used for (b) (4) products is performed in accordance with (b) (4) and provides assurance of sterility for the matrix represented by the sample. A sample is (b) (4)

Sterility Test Qualification for DP
The Sanofi DP was qualified using the (b) (4) method by performing B&F qualification studies to demonstrate the MenQuadfi™ DP does not inhibit bacterial and fungal growth. Sanofi performed the test using (b) (4) indicator microorganisms (i.e., (b) (4) and one known environmental strain (i.e., (b) (4)) on (b) (4) of MenQuadfi™ DP.

The test for each microorganism was performed using (b) (4) of MenQuadfi™ DP (b) (4)

(b) (4)

After review of sterility method qualification results, this reviewer concludes this method was qualified in accordance with (b) (4) and the test results indicate there is no product inhibition on microorganism growth.

18. Endotoxin Test (Hyesuk Kong)

(b) (4) Bacterial Endotoxin Test ((b) (4) BET) Method

(b) (4) BET is performed to detect or quantitate bacterial endotoxins that may be present in or on the subject samples to which the test is applied. (b) (4)

(b) (4)

(b) (4) BET Qualification for DP

Sanofi qualified their (b) (4) BET method for MenQuadfi™ DP to demonstrate their method is suitable under the actual conditions of use in accordance with (b) (4) .

(b) (4)

Sanofi submitted bacterial endotoxin concentration results of several DP lots and all were found to be within their proposed release specification of (b) (4) . CBER finds their proposed BET release specification of (b) (4) acceptable.

Based on the data presented in their report, MenQuadfi™ (b) (4) DP did not exhibit any inhibitory or enhancement factors that would adversely impact the (b) (4) test. After review of (b) (4) BET method qualification results, this reviewer concludes this test method was performed and compliant with (b) (4) .

Conclusion

After a thorough review of the information submitted in this BLA, this reviewer finds Sanofi's bioburden, sterility, and endotoxin test method qualifications were performed in accordance with (b) (4) and determined the results provide evidence of method suitability under the actual conditions of use. Therefore, this reviewer recommends approval.