DEPARTMENT OF HEALTH & HUMAN SERVICES

Food & Drug Administration
1401 Rockville Pike
Rockville, MD 20852

MEMORANDUM

Date: January 20, 2010

To: Willie F. Vann, Ph.D. HFM-437
Chair, Menveo BLA Review Team

From: Rajesh K. Gupta, Ph.D., HFM-407
Deputy Director, Division of Product Quality (DPQ) and
Acting Lab Chief, Product Quality Laboratory Staff, DPQ

Through: William McCormick, Ph.D., HFM-407
Director, Division of Product Quality (DPQ)

Subject: STN 125300: Meningococcal ACWY Conjugate Vaccine, Menveo®, Novartis – Review of Drug Substance and Drug Product Analytical Procedures

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Review of the analytical procedures and the associated validation protocols and reports was performed by the staff of Division of Product quality (Reviewers from DPQ: Rajesh K. Gupta, Alfred Del-Grosso, James Kenney, Manju Joshi, Hsiaoling Wang, Nora Etz, Joe Progar, and Brandon Duong). Specifications for methods used to release Drug Substance and Drug Product were also reviewed.

SUBMISSIONS REVIEWED

STN 125300/0, Sections 3.2.S.4 (for CRM_{197}, MenA Polysaccharide, MenC Polysaccharide, MenW Polysaccharide, MenY Polysaccharide, MenA CRM Conjugate, MenC CRM Conjugate, MenW CRM Conjugate and MenY CRM Conjugate), and 3.2.P.5 (for MenCWY Liquid and MenA Lyophilized)

STN 125300/0.4 received on January 15, 2009

STN 125300/0.5 received on February 6, 2009 (Submission of Lot Release Protocol Template)

STN 125300/0.11 received on May 6, 2009 (submission of results for samples received for in-support testing)

STN 125300/0.14 received on June 22, 2009

STN 125300/0.15 received on August 21, 2009

STN 125300/0.16 received on October 8, 2009 (Proposal for submitting another set of samples for in-support testing)

STN 125300/0.17 received on November 25, 2009 (submission of results for samples received for in-support testing)

METHODS REVIEWED

Polysaccharide-CRM_{197} Conjugates (Drug Substance, MenA-CRM, MenC-CRM, MenW-CRM and MenY-CRM)

---b(4)----------
---b(4)----------
---b(4)----------
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-----b(4)----------
---b(4)----------
--b(4)-------
---b(4)----------
---b(4)----------
---b(4)----

MenA Lyophilized Conjugate (Drug Product)

Identity ---b(4)----
-----b(4)----------
-----b(4)----------
Protein Concentration -b(4)-
Endotoxin
Sterility
General Safety
Residual Moisture
---b(4)----
----b(4)----------

MenCWY Liquid Conjugate (Drug Product)

Identity ---b(4)----
Identity ----------b(4)----------
Men C ---b(4)----
Men C ---b(4)----
Men W ---b(4)----
Men W ---b(4)----
Men Y ---b(4)----

Men Y --b(4)---------
Endotoxin
Sterility
General Safety

RECOMMENDED ACTION

The data submitted to support the analytical methods used for testing of Drug Substance (DS) and Drug Product (DP) of Meningococcal ACWY Conjugate Vaccine, Menveo®, and specifications proposed for release of DS and DP were reviewed. A number of issues with regard to analytical methods, adequacy of analytical methods validations and proposed specifications were found in the original submission. A complete response letter including these issues was sent to sponsor on June 25, 2009. The sponsor addressed all the issues related to analytical methods, methods validations and specifications in amendment 0.15 to the BLA. Based on the review of original submission and amendments related to analytical methods cited above, I recommend approval of this application. Amendments related to lot release protocol, 0.5 and to testing in support of the BLA, 0.11, 0.16 and 0.17 are not discussed in this review. The Lot release protocol is being finalized with the sponsor and separate test memos for in-support testing will be submitted to the record.

DETAILED REVIEW AND COMMENTS

Based on the review of the original submission, an information request for clarifications and additional documents was submitted by Dr Cara Fiore in an email on May 22, 2009. Novartis provided the required information in amendment 0.14 June 22, 2009. A number of other issues with regard to the analytical methods, adequacy of the analytical methods validations and proposed specifications were communicated to the sponsor in a complete response letter on June 25, 2009. The sponsor addressed all the issues related to analytical methods, method validations and specifications in the submission 0.15. This review provides an initial review of all methods listed above and includes CBER's comments and Novartis's response to CBER's comments. CBER's final review and conclusion about the suitability of the method for intended use is then provided.

A. General Comments on Methods, Method Validations and Specifications

1. Organization of Application and Errors (Question 8 in the CR Letter)

a. Sections on "Validation of Analytical Procedures" were not organized in a manner to provide clear interpretation from the documents submitted. Documents from multiple serogroups of *N.meningitidis* were submitted under "Method Validation section" for a single serogroup. These documents do not provide the purpose and scope of the studies performed, making it impossible for the reviewer to interpret the scope of the studies performed

beyond the serogroup for which these studies were primarily performed. In addition, multiple revisions of validation protocols and reports have been submitted without any details on the changes in the multiple revisions. For example, for the test for --b(4)---------- in Drug substance polysaccharides, 14 documents have been provided for MenA polysaccharide and 8 documents each for MenW and MenY polysaccharides.

In the summary document for each analytical method, for example, section 3.2.S.4.3.1.5 “Analytical Validation: -b(4)-------,” the purpose and scope of each study for the particular serogroup for which these documents are submitted should be explained clearly. CBER asked Novartis to - Please provide all method validation reports with details on purpose and scope of various documents, as well as any revisions. If multiple revisions of a document are submitted, details about changes in the revision and purpose and scope of earlier versions should be provided.

Novartis Response (Amendment 0.15)

Novartis has performed a critical review of the above mentioned sections, with the following determinations and revisions.

Narrative

Novartis considers the narrative part of each 3.2.S.4.3 and 3.2.P.5.3 sections clear and complete for the purpose of review. Therefore, unless changes derived by the re-performing of the linearity (see Question 6c) were necessary, no modification was made to these parts.

Analytical Method Validation Protocols and Reports

Novartis recognizes that documents attached to each 3.2.S.4.3/.P.5.3 section were not clearly identified with regard to their purpose and scope. For this reason, at the beginning of each 3.2.S.4.3 and 3.2.P.5.3 section, we introduced a table describing in detail each document attached. This table replaces the list of attachments, present in the original documents. Template of the table was included in the response.

Novartis considers that this presentation of the attachments will clarify the reason why a document is attached to that particular section.

In addition, in many cases a redundant number of protocols/reports (not relevant for the method treated in that particular section) were attached to a single method section. This was originally done with the aim of providing comprehensive information to the Agency, however Novartis recognizes that the rationale for inclusion of specific documents was not always clear. Therefore, Novartis reassessed the necessity of each attachment

for each of 4.3/5.3 sections and maintained only the attachments related to the relevant method for the relevant serogroup.

In summary, we maintained only the protocol and report related to MenC --b(4)--------. Originally, four documents were attached because in the b(4) 07.027 QP1 Rev.0, cross-reference was made to b(4) 07.027 VR1 Rev.0 MenA polysaccharide for the assessment of --b(4)---------- and Novartis attached the report -b(4)-07.027 VR1 Rev.2 and the relevant protocol for MenA. Novartis recognizes that these documents did not provide valuable information and could be confusing. So, instead of attaching these documents to the MenC section, a reference has been made to the relevant MenA section, where the most updated report and protocol is attached, containing complete information.

In addition, we also performed a quality check of the protocols and reports submitted and, in the introduction document of each 4.3/5.3 sections, we have inserted a table (named "errata corrige") to trace and correct translation and/or typographical error.

Novartis considers that the 3.2.S.4.3 and 3.2.P.5.3 sections, with these modifications, are now clear and organized in a manner that would allow a meaningful and effective review.

DPQ's Review of Novartis Response

The new format of presentation of various validation documents is acceptable.

b. There are translational and /or typographical errors that make it difficult to make complete and accurate interpretations from the documents and also slow the review process significantly. A few examples of such errors are given below. Please perform a quality check of the entire submission to correct all errors or omissions.

- In SOP 201700-03 (-b(4)- 07.062), page 5, line 8, "--b(4)----------
- In SOP 201707-02(-b(4)- 07.139), --b(4)----------This statement is incomplete/unclear and difficult to interpret without missing text.
- Regarding the section 3.2.P.5.2,1.2 Identity Men W-CRM and MenY-CRM of document 3.2.P.5.2 "Analytical procedures Menveo® , MenCWY Liquid" Page 5 and 6: On page 6,it is stated that the described procedure for identity of MenW-CRM and MenY-CRM ---b(4)----------.

Please comment why MenA ---b(4)----------

- Please clarify why document 2.3.S.4 Control of Drug Substance, MenC polysaccharide, page 4, section 2.3.S.4 mentions MenA polysaccharide, when this document and this section are for MenC polysaccharide.
- Please clarify why b(4) of polysaccharide MenA, MenC, MenW, MenY---b(4)----- SOP 202138 VP.4 Rev.0 contains the validation protocol for b(4) determination of MenC when limit value is for MenW on page 1.

Novartis Response (Amendment 0.15)

As for the previous response 8a), Novartis performed a quality check of all translated SOPs submitted with the original BLA. In section 2.3.R.3 Method Validation Package, a table (named "errata corrige") is inserted to trace and correct all translation and/or typographical errors.

In addition, Novartis performed a quality check of all 3.2.S.4.2 and 3.2.P.5.2 sections originally submitted. A number of translational and typographical errors were identified. Details of correction made following the quality check are provided in the Attachment 0015Q8b.1 (Analytical Methods Errata Corrige).

Consequently, all 3.2.S.4.2 and 3.2.P.5.2 sections of the dossier were updated and are submitted. Where applicable, relevant replacement sections of 3.2.P.5 (Control of Drug Product) and 3.2.S.4 (Control of Drug Substance) are also provided.

DPQ's Review of Novartis Response

The response is adequate. A list of corrections as "Errata Corrige" has been useful and corrected documents are easy to review without the risk of misinterpretation.

2. Specifications of Drug Substance and Drug Product (Question 5 in the CR Letter)

The following lot release and stability specifications are not adequately justified. Please comment on the rationale for the following testing specifications:

a. Specifications for --b(4)--------: The specifications for --b(4)----------are not consistent among the four conjugates; i.e., the MenA conjugate has different specifications than MenC, MenW and MenY, despite having similar precision for --b(4)---------- results for all four serogroups. Specifications for MenA conjugate have been set at -b(4)- of the target --b(4)---------- of

--b(4)-----, whereas specifications for MenC, MenW and MenY conjugates have been set at -b(4)- of target --b(4)---------- Based on the data from lot release testing and stability and precision of test for --b(4)----------, a specification of greater than -b(4)-- of target concentration for all serogroups is not justified. Please consider revising the specification for --b(4)---------- for MenC, MenW, and MenY to not greater than -b(4)- or provide a justification for current specification of -b(4)-

Novartis response (Amendment 0.15)

---*b(4)*---------- ----------

---*b(4)*--- ----------

----*b(4)*----- ----------

---*b(4)*---- ----------

----*b(4)*---- ----------.

DPQ's Review of Novartis Response

Novartis response on the specifications of --b(4)---------- for MenC, MenW and MenY conjugates at -b(4)- is adequate.

b. Specifications for --b(4)---------, which is a critical parameter to ensure potency of vaccine during its shelf life is set at -b(4)-- We

do not consider this specification justified based on lot release testing and stability data submitted. These data do not justify setting specifications at more than --b(4)-----------------. Please consider revising the specification for --b(4)----------- to not greater than b(4) or a value that is more consistent with the data submitted in the BLA.

Novartis Response (Amendment 0.15)

The limit -b(4)--- for percentage of --b(4)----------- in Drug Product (MenA Lyo and MenCWY Liquid both for release and stability), proposed by the Company, was set considering the characteristics of the products, rather than the actual process capability to produce product that is consistently in a certain range, considering also the limited number of batches produced so far.

----b(4)---- --

--b(4)--- ---.

---b(4)--- --

--b(4)-------------------------

Differences of --b(4)---------- for the MenC component in the Drug Product at --b(4)--- and in the respective Drug Substances are around b(4) this can be considered as the maximum --b(4)----- measured, i.e., a --b(4)-------- over release at the end-of-shelf-life. Accordingly, release specification limit for MenC -b(4)---------- in the MenCWY component would be set at --b(4)------ the stability specification limit -b(4)- that is -b(4)-

Differences of --b(4)---------- for the MenW component in the Drug Product at -b(4)------ and in the respective Drug Substances are around -b(4)- this can be considered as the maximum --b(4)--- measured, i.e., an --b(4)----- over release at the end-of-shelf-life. Accordingly, release specification limit for MenW --b(4)---------- in the MenCWY component would be set at --b(4)------- the stability specification limit -b(4)----- that is -b(4)----

Differences of --b(4)---------- for the MenY component in the Drug Product at -b(4)---- of storage and in the respective Drug Substances are around -b(4)- this can be considered the maximum -b(4)-- measured, i.e., a --b(4)------- over release at the end-of-shelf-life. Accordingly, release specification limits for MenY --b(4)---------in MenCWY component would be set at --b(4)----- the stability specification limit -b(4)---- that is --b(4)---

Considering the following:

-the three proposed limits have been calculated as "worst case" , but the actual values related to the ----b(4)---------- cannot be known due to the fact that the methods used to do this test have an intrinsic variability and a limited sensitivity -the "strength" (stability) of the conjugated product is comparable among the different serogroups .

Novartis proposes a unique limit applicable to MenC, MenW, and MenY that is the average limit of the worst case limits above reported (--b(4)----------)

New proposed limit -b(4)-

Moreover, since:

-no --b(4)---------- is expected through the formulation and filling process of this liquid product

-no significant -b(4)----- has been ever observed for the respective Drug Substances during the storage,

-the same limit mentioned above is applied to the release and stability specifications of the drug substances.

MenA Lyo component:

Differences of --b(4)---------- in the Lyo Drug Product at -b(4)---------- of storage and the respective Drug Substance (assuming – as worst case- this as zero, since the data are usually reported as "NMT" the limit of the assay) can be estimated as -b(4)- that can be considered as the maximum --b(4)------- measured, meaning the

maximum increment of this parameter at the end-of-shelf-life. Accordingly, release specification limits for the MenA Lyo component would be set --b(4)----- the stability specification limit -b(4)---- that is as --b(4)----

Moreover, since:

--b(4)---------- through the formulation/lyophilization process is expected to be --b(4)---------- (as worst case)

No significant -b(4)---- has been ever observed for the MenA-CRM Drug Substances during the storage,

a limit of -b(4)--- (calculated as --b(4)-- will be applied to the release and stability specifications of the MenA-CRM --b(4)----------

Conclusion

Summary of the --b(4)---------- specifications for drug product and drug substances has been reported in the Tables 5-1 and 5-2.

These new release limits have been calculated to guarantee that the drug product will meet --b(4)----- criteria also at the end-of-shelf-life.

Novartis plans to implement the new ----b(4)----------

The company considers that lots manufactured prior to introduction of the new limit are releasable.

Novartis has established a manufacturing process that is capable of yielding products with a consistently ----b(4)---------- and the product is sufficiently stable to assure such --b(4)------- throughout the proposed shelf life.

In conclusion, Novartis believes that the herein proposed specification limits for --b(4)---------- are adequately set considering the nature of the glycoconjugate molecules and the amount of data available now.

DPQ's Review of Novartis Response

Revised release specifications for DP for ----b(4)---------- for MenC, MenW and MenY conjugates and at b(4) for MenA conjugate and stability specification of -b(4)- for all 4 conjugates are acceptable.

Revised release specifications for DS for --b(4)---------- for MenC conjugate, at -b(4)- for MenW and MenY conjugates and at b(4) for MenA conjugate and stability specification of -b(4)---- for MenC, MenW and MenY conjugates and at -b(4)- for MenA conjugate are acceptable.

Since the original proposed specification of --b(4)----------for all 4 types of conjugates is consistent with the -b(4)---

-------specifications for other glycoconjugate vaccines, the sponsor's proposal to release lots manufactured prior to introduction of new specifications is acceptable. Tighter new specifications are consistent with process capability.

c. The specifications for protein concentration (-b(4)-------) of Drug Product, Menveo, MenA Lyophilized has a wide range, and Menveo, MenCWY Liquid does not have any specifications for total protein. Please set total protein specifications for Menveo, MenCWY Liquid and please consider setting the total protein specifications with a more narrow range for Menveo, MenA Lyophilized.

Novartis response (Amendment 0.15)

The dosage of the vaccine is based on the --b(4)---------- (not the protein content) of the drug substances and, accordingly, there are specifications for --b(4)---------- of each conjugate component. Likewise, for each conjugate component, there is a specification range for the --b(4)----------). Having provided upper and lower limits for both the --b(4)----------), the allowable protein ranges are thus fixed.

The MenA drug product component is freeze-dried -----(b)(4)------

In the following a detailed justification for the total protein specification range of the MenA Lyo component is provided. Furthermore, an assessment of the total protein ranges that can be expected in the MenCWY component is given. As explained above, testing for total protein of this drug product component is not considered necessary.

MenA Lyophilized

The specification range for MenA --b(4)---------- per vial and the --b(4)---------- of the drug substance is set between --b(4)----. The lowest potential protein content is therefore -b(4)----------; the highest potential protein content is ---b(4)----------. Since the range of the protein specification is dependant

on the range of the ---b(4)---------- specification, the limits for protein cannot be narrowed without reducing the range for --b(4)--------- in the drug substance.

MenCWY Liquid

As already mentioned above, ----------(b)(4)---------- ----------, and is strictly linked to the --b(4)---------- and does not change during the formulation process. The allowable range for the drug product protein concentration can be calculated as --b(4)---------- considering the maximum and minimum of --b(4)---------- and --b(4)-------- as in Table 5-3 of amendment 0.15.

In summary, because the --b(4)---------- is fixed, the --b(4)---------- and protein contents are not independent parameters.

DPQ's Review of Novartis Response

Novartis explanation on the role of protein specifications for MenA conjugate and the complexity in setting specification for MenCWY is adequate. Novartis' response on the non-significance of total protein specifications for MenCWY conjugate and control of the product through the ---b(4)---------- is acceptable.

d. Specifications for endotoxin of the Drug Product ---b(4)------- MenA Lyophilized conjugate and --b(4)--------- for MenCWY Liquid) are not supported by the data submitted. These specifications should be based on the data and manufacturing process capability. Please either submit the data on which the endotoxin specifications are based, or revise and justify the specifications based on the data in the BLA.

Novartis response (Amendment 0.15)

*-----b(4)---------- ----------

---*

----b(4)---- ---

DPQ's Review of Novartis Response

Novartis response on specifications for endotoxin is adequate.

e Purity specification for CRM_{197} has been described as -b(4)- Data reported from all lots have purity reported as not less than -b(4)- Please justify a specification of -b(4)- or consider setting purity specification, based on data in the BLA, at -b(4)-

Novartis response (Amendment 0.15)

The current specification for purity of CRM_{197} is based on --b(4)---
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--------------- *Novartis has a broad experience with the manufacturing and testing of CRM_{197}; this protein is used in the production of other conjugate vaccines. In these vaccines, the specification for purity for CRM_{197} is set as b(4) In Table 5-4 of amendment 0.15, the purity data obtained for CRM_{197} lots manufactured in Rosia have been summarized.*

The process capability analysis performed on all data shows that, with actual specification limits, none of the lots analyzed is out of specification. The lowest data point obtained until now is -b(4)- Based on this analysis, Novartis will introduce an action limit defined by the ------------b(4)-------------------------------------- ------

--b(4)---------- This limit is b(4). Valid and within-specification results below this action limit will trigger an investigation. In this way, process performance will be monitored closely. Therefore, Novartis will maintain the specification of -b(4)-- for purity of CRM_{197}.

DPQ's Review of Novartis Response

Novartis proposal to introduce an action limit at -b(4)- purity of CRM_{197} and retaining the specifications at -b(4)- is acceptable.

3. General Comments on Methods Validations (Question 6 in the CR Letter)

Several process and release methods have not been properly validated. Please address the following comments on the Method Validations.

a. --b(4)---------- content, MenW and MenY Report -b(4)---------- is the most critical step to assure the accuracy and utility of the test for -b(4)----------. There are no data presented in the validation report to demonstrate that --b(4)---------- Please provide evidence that --b(4)----------

Novartis Response (Amendment 0.15)

-----b(4)----- ----------

----b(4)----------------- --

DPQ's Review of Novartis Response

Recovery of --b(4)-------------------------- between -b(4)-------- demonstrates accurate ---b(4)-- The response is adequate.

b. Accuracy Studies were not properly evaluated as illustrated in the examples below. Further, accuracy studies should be evaluated by calculating recovery of the spiked quantity of materials, not from total of starting sample plus spiked material. Please recalculate spike recovery for all methods for Drug Substances and Drug Products.

Novartis Response (Amendment 0.15)

CBER has requested that the percentage recovery in the accuracy tests be calculated according to Equation 1 below:

{[(Amount measured in spiked sample) – (Amount measured in unspiked sample)]/(Amount in spike)} X 100.
This formula had been applied to the accuracy studies presented in Table 6b-16 of amendment 0.15.
The exceptions for which Equation 1 were not utilized are:

----b(4)---- ---

The results of the recalculations are shown in the following sections. Please recall that the --b(4)------- was the only one that was ever used for MenA and MenC, whereas for MenW and MenY, the initial --b(4)-------- method has been replaced by the -b(4)- method. Recalculations of -b(4)------- percentages using Equation 1 are presented for both methods, when applicable.

A. ---b(4)------------------------- MenA in sample of MenA lyo -b(4)- 07.023 (202152)

The --b(4)-------------------------------- recovery percentages, as determined by the --b(4)---------- method, were recalculated, according to Equation 1.

The results are summarized in tables provided in amendment 0.15 and given in the report 202152 VR 2 Rev. 5. These data are quoted to 4 decimal places due to the readouts from the instrumentation used for these determinations. Novartis appreciates that this level of precision is artificial and may revise the values to two decimal places if the opportunity presents. This would not change the conclusions of the validation.

Suitability of the method has been shown.

B. ---b(4)---------------------------- MenW and MenY in samples of MenCWY liquid (-b(4)- 07.029)

The results shown in this section were derived from the --b(4)--------- method. For --b(4)--------- determination, the accuracy data presented in the validation report b(4) 07.029 VR 1 Rev. 3 are fully compliant with CBER's request, being calculated by using the Equation 1.

For --b(4)---------- the recoveries were recalculated using Equation 1. Results are reported in the Tables 6b-3 and 6b-4, provided in the amendment 0.15.

----b(4)---------------------- ----------

----------b(4)----------

The percentage recovery calculation was made by using the formula Equation 1:

As can be seen in Tables 6b-5 and 6b-6, the method performance is improved and shows satisfactory accuracy.

The validation study showed that the new method fulfills the predefined acceptance criteria for --b(4)---------- recovery percentage. In addition, Novartis performed a study testing in parallel several batches with the two methods. The study included batches ----------b(4)---------- tested at -b(4)--- of shelf-life. Results are shown in Table 6b-7 of amendment 0.15. In all but one case, the measured levels were below the limit of quantitation (LOQ) for both methods. The exception was one result that was just above the LOQ.

C. --b(4)---- MenC --b(4)---------- in samples of MenCWY liquid (b(4) 07.030)

The validation reports submitted with the BLA show recovery values which had been calculated using Equation 2 as shown below. Each test met its predefined acceptance criterion for recovery.

----b(4)----- ----------

3 Pages determined to be not releasable:
b(4)

b (ii) ----b(4)---------- ----------

--------**b(4)** ----------

---*b(4)*--- ----------

--b(4)- ----------

Sponsor's response for not measuring --b(4)-------- and therefore not using it as a spike in the accuracy studies is adequate.

b (iii) -b(4)------ MenA-Lyophilized, b(4) 07.155 VR.2 Rev.0 - In the evaluation of accuracy, please report actual unspiked and spiked sample results in µg/ml -b(4)--- in addition to % recovery results.

Novartis Response (Amendment 0.15)

The last revision of the report b(4) 07.155 VR 2 Rev. 3 reports the unspiked and spiked sample results in mcg/ml in addition to recovery % results.

DPQ's Review of Novartis Response

Sponsor's response is adequate.

c. Several submitted analytical validation studies evaluate procedural range based on linearity of the standard curve. As recommended in ICH Q2(R1), "Validation of Analytical Procedures", the range of a procedure is established by confirming that the analytical

procedure provides an acceptable degree of linearity, accuracy and precision when applied to samples containing amounts of analyte within or at the extremes of the specified range of the analytical procedure. Please confirm that the procedural range for all methods used for release testing of Drug Products and Drug Substances are as described in the ICH Q2(R1). During our review we have found examples that may not meet the recommendation in ICH Q2(R1). For example:

---b(4)---- ----------

Novartis Response (Amendment 0.15)

According to the ICH guideline, the range is established confirming that the analytical procedure provides an acceptable degree of linearity, accuracy and precision when applied to the samples containing amounts of analyte within or at the extremes of the specified range of the analytical procedure. For the --b(4)----------, the samples are always ---b(4)----------

For the -b(4)--, according to the b(4) guideline and according to our internal SOP -b(4)- 11.028, the range is not prescribed.

The company confirms that the range is determined according to the ICH guideline. ---b(4)--- ----------

Methods currently used for Drug Substance and Drug Product are listed below. For each method, the range of the method and the limit of specification are given. The range was reported in the relevant validation report. Tables 6c-1 to 6c-6, presented in amendment 0.15, and showed methods and specifications for monovalent bulks conjugates (DS) and DP.

Note 1: The validation reports 226491 VR 5, 226491 VR 6, 226491 VR 7, 226491 VR 8 regarding the --b(4)---- ----------

----------b(4)----------

-----b(4)----------

DPQ's Review of Novartis Response

----b(4)--- ----------

d. You have demonstrated linearity of analytical methods from the standard curve. Linearity across the range of method should be demonstrated using samples for which the method is to be used. This has been observed for all the method validations submitted with this application. Please perform additional studies to demonstrate linearity across the range of the method with appropriate samples for all methods used for release testing of Drug Products and Drug Substances.

Novartis Response (Amendment 0.15)

Novartis performed all linearity tests of quantitative methods using appropriate samples for which the method is to be used. These methods are, for Drug Substances, MenA-CRM, MenW-CRM, MenY-CRM, MenC-CRM and, for Drug Products, MenA lyophilized conjugate component and MenCWY liquid conjugate component.

The curve was constituted by the specified samples at --b(4)----------, as described in the reports. Where the --b(4)---------- ----------

The methods for which the linearity tests were repeated are listed below in Table 6d-1 (presented in amendment 0.15). The respective protocols and reports were reviewed and attached to the relevant 3.2.S.4.3 and 3.2.P.5.3 sections (see Question 8 a)

DPQ's Review of Novartis Response

Defining linearity of methods listed in Table 6d-1 of amendment 0.15 using samples is acceptable.

e. We have the following questions regarding the validation of the -b(4)-- method used as an identity test as is cited in the following documents:

----b(4)--- ----------

e (i) Validity criteria for the analysis/evaluation of results, as per SOPs (SOP 201717-03 [b(4) 07.209] and SOP 201711-02 [b(4)-07.166]), state that the ----b(4)----------. This high blank value is not supported by the data submitted. Please reevaluate this parameter for the identity test.

Novartis Response (Amendment 0.15)

Novartis has evaluated the blank in the test methods described in the three SOPs (b(4) 07.209; b(4) 07.166; b(4) 07.190) used for identity test. A statistical analysis of the blank was performed as reported in the technical report 264053-01 (MenA-CRM).

A new method validation using the new acceptance criterion for the blank was performed. This applies also to the answers given to Question 6e, subparagraphs ii, iv, v and vi. The results obtained are reported in the validation studies listed below:

----b(4)--- ----------

----b(4)--- ----------

----b(4)--- ----------

----b(4)--- ----------

-b(4)- 07.190 VR 3 Rev. 0 (3.2.P.5.3 MenCWY liquid)

The new acceptance criteria were met.

DPQ's Review of Novartis Response

Novartis approach in defining blank and resulting re-validation studies are acceptable.

e (ii) The limits for positive and negative controls are not sufficiently different to provide a clear distinction between these positive and negative controls. SOPs (201717- 03 [-b(4)- 07.209]) Identity and -----b(4)---------- method (applies to CRM-MenA, -MenW and -MenY) and 201711-02 [b(4) 07.166] Identity of --b(4)--------- CRM-MenC--b(4)---- method), validity criteria for analysis of positive and negative controls (Section 4.5 of SOP 201717-03 and section 4.7 of SOP 201711-02) state:

- The mean of b(4) of the positive control must be --b(4)----- (SOP 201717-03 for CRM-Men W and CRM-MenY) -b(4)---------- (SOP 201711-02 for CRM-MenC) the mean b(4) of the blank.
- The mean b(4) of the negative control must not ---b(4)---------- (SOP201717-03 for CRM-MenA, CRM-MenW and CRM-MenY) --b(4)-- (SOP 201711-02 for CRM-MenC) the mean b(4) of the blank.

These criteria could result in too small a difference between positive and negative samples or controls in a valid assay. Please re-evaluate validity criteria for positive and negative controls so that there is a more distinct (i.e., greater) difference in responses for these controls.

Novartis Response (Amendment 0.15)

Novartis has revised the three SOPs (b(4) 07.209; b(4) 07.166; b(4) 07.190) used for the identity test, in order to re-evaluate the acceptance criteria for positive and negative controls.

As a consequence, for all three methods, new acceptance criteria were reported, according to a statistical evaluation study given in the technical report 264053-01 (MenA-CRM).

In summary:

b(4) 07.209

The ratio between the mean of the positive control --b(4)------ and the mean of the negative control --b(4)----- must be b(4)

b(4) 07.166 and b(4) 07.190

The ratio between the mean of the positive control --b(4)------ and the mean of the negative control --b(4)------ must be b(4).

The methods were re-validated considering these new acceptance criteria and the results obtained are reported in the validation studies listed below:

---------b(4)----------

---------b(4)----------

---------b(4)----------

---------b(4)----------
b(4) 07.190 VR 3 Rev. 0 (3.2.P.5.3 MenCWY liquid)
The new acceptance criteria were met.

DPQ's Review of Novartis Response

The new criterion for the positive and negative controls is consistent with the data and re-validation studies are adequate.

e (iii) The specificity of --b(4)---------- used in -b(4)--- assays needs to be qualified for all serogroups. You have provided a qualification report for the --b(4)--- to the meningococcal group A --b(4)----- however, such qualification reports for other serogroups could not be located in the submission. Please provide the qualification reports for the meningococcal groups C, Y, and W-135. Please also provide data to confirm that the ---b(4)----------

Novartis Response (Amendment 0.15)

The qualification reports confirming the specificity of --b(4)----- used in --b(4)------ test for the meningococcal C, Y and W-135 -b(4)----- have been provided as attachments to the relevant Analytical Validation sections.
The following update sections are submitted:
3.2.P.5.3.1.1 MenCWY Liquid Identity MenC-CRM - -b(4)- 07-033 Rev. 0
3.2.P.5.3.1.2 (MenCWY Liquid) Identity MenW-CRM and MenY-CRM - -b(4)- 06-048 Rev. 1 and -b(4)- 08-054 Rev. 0.

DPQ's Review of Novartis Response

Qualification studies on --b(4)---- for C, Y and W-135 used in the identity test are adequate.

e (iv) -----b(4)---------- ----------

---------b(4)----------

Novartis Response (Amendment 0.15)

As mentioned previously, Novartis performed a new validation of the identity tests for ---b(4)----------) and drug product (MenCWY liquid and MenA lyophilized) in order to check the ---b(4)----------

The results, given in the following reports, confirmed the specificity of the methods as all ----b(4)---------- were positive, while all ---b(4)----------.

----b(4)----------
----b(4)----------
----b(4)----------
----b(4)----------
--b(4)--07. 190 VR 3 Rev. 0 (3.2.P.5.# MenCWY liquid)

DPQ's Review of Novartis Response

Novartis performed a new validation of the identity test by -b(4)-- The response is adequate with regard to specificity of each -b(4)---- used in the identity test.

e (v) Validation report -b(4)-07.166 VR3 Rev. 0 for one of the -b(4)--- assays (Page 26 of 110 in report) has the blank b(4) values -b(4)- As per the validation criteria for this test, specified in the SOP, this test should be deemed invalid. Please clarify if this test was used to generate results.

Novartis Response (Amendment 0.15)

Novartis acknowledges this comment and agrees that this specific analysis present in the validation should have been declared invalid and repeated since the blank b(4) was -b(4)-
Considering that it was impossible to repeat the test on the same samples used in the original validation studies, Novartis repeated the complete method validation, without introducing any operative method changes, but only modifying acceptance criteria, per CBER's request (Question e, subparagraphs i and ii).

The results are reported in b(4) 07.166 VR 6 Rev. 0 (3.2.S.4.3 MenC-CRM) and show that the method was successfully validated.

DPQ's Review of Novartis Response

The response is adequate.

e (vi) Validation report b(4) 07.166 VR3 Rev. 0 shows two tests with large differences in -b(4)------- values for blank, ---b(4)-------------
----

--. Are these differences typical for this assay? Please comment.

Novartis Response (Amendment 0.15)

As reported herein, a statistical analysis of the blank, positive control and negative control results has been performed.
As given in the technical report 264053-01 (MenA-CRM) (appendix 1), the variability observed is acceptable for a qualitative method, such as the identity test.

DPQ's Review of Novartis Response

The response is adequate.

e (vii) In validation report b(4) 07.166 VR3 Rev. 0 , section 4.2, the Acceptance Criteria for Limit of Detection is defined as the -b(4)-- ----------------------------. Please define in a quantitative manner what is meant in this context by the term "--b(4)-----------

Novartis Response (Amendment 0.15)

----*b(4)*------------------------------------- -------------------------------
----

DPQ's Review of Novartis Response

The response is adequate.

B. Specific Comments on Methods for Drug Substance and Drug Product

1. Test for ---------b(4)----------------------------------- on MenA-CRM Conjugate on DS and DP

----b(4)---- --

--b(4)---- --

Documents reviewed, SOP 202152, b(4) 07.023 VP1 Rev. 2 and 202152 VR1 Rev. 2, 202152 VP2 Rev. 5 and 202152 VR2 Rev. 5.

DPQ's Comment (Question 7b in the CR letter)

--b(4)---- --

Novartis Response (Amendment 0.15)

--*b(4)*--- ----------

DPQ's Review of Novartis Response

----b(4)--- ----------
----------.

DPQ's Comment (Question 7c in the CR letter)

---b(4)--- ----------

Novartis Response (Amendment 0.15)

---*b(4)*---- ----------

DPQ's Review of Novartis Response

The response is adequate.

DPQ's Comment (Comment 2 in Information Request dated May 22, 2009)

Regarding the --b(4)---------- content, MenA Conjugate, Report 202152 VR2 Rev. 3:
In the evaluation of --b(4)-------- accuracy, it states that samples were -b(4)-- with MenA standard. Please clarify if the sample preparation step described in SOP 202152-07, Section 4.3.2, using the --b(4)---------- was included as part of this evaluation to allow an assessment -b(4)----------

Novartis Response (Amendment 0.14)

--b(4)--- ----------

DPQ's Review of Novartis Response

The response is adequate.

DPQ's Comment (Comment 5 in Information Request dated May 22, 2009)

Regarding SOP 202152-07 "Quantitative determination of the --b(4)---------- in CRM-MenA glycoconjugates"

i. Section 4.2 (S1) states that "The --b(4)----------". Please specify the method and calculations used in this qualification.
ii. Section 3 – -b(4)------ MenA Polysaccharide Standard"; please describe the source of this material and methodology that was used to characterize and standardize it (or refer to an SOP or protocol in the BLA).
iii. Section 3 – Materials and Equipment; ---b(4)----------

Novartis Response (Amendment 0.14)

---*b(4)*---- ----------

DPQ's Review of Novartis Response

The responses are adequate.

Conclusion

Based on Novartis responses, discussed above and also in section A.3 of this review memo on method validation comments, the -b(4)---------- and --b(4)---------- method used for MenA-CRM conjugate in DS and DP is suitable for intended purposes.

2. Test for --b(4)---------- on Men-C CRM Conjugate in DS

--b(4)---- ----------

DPQ's Comment (Question 7a in the CR letter)

----b(4)--- ----------

Novartis Response (Amendment 0.15)

---*b(4)*--- ----------

DPQ's Review of Novartis Response

The response is adequate.

Conclusion

The method used for ----b(4)---------- in MenC-CRM conjugate (DS) is suitable for intended purpose.

3. Test for --b(4)---------- on MenC-CRM conjugate in DS

----b(4)--- ----------

------------b(4)----- --

Documents reviewed, SOP 202786-06, b(4) 07.007 VP3 Rev. 3, b(4) 07.007 VR3 Rev. 3, b(4) 07.007 VR1 Rev. 1 and b(4) 07.007 VR1 Rev. 1 addn.

Conclusion

After addressing the method validation issues (discussed in Section A.3 of this review memo, the method used for --b(4)------------------------------ in MenC-CRM conjugate (DS) is suitable for intended purposes.

4. Test for --b(4)-------------------------- on MenC-CRM conjugate in DP

-----b(4)---- ---

Documents reviewed, SOP 202157-06, 202157 VP2 Rev. 1, 202157 VR2 Rev. 0 and 202157 VR2 Rev. 1

Conclusion

After addressing the method validation issues (discussed in Section A.3 of this review memo, the method used for ----b(4)----------in MenC-CRM conjugate (DP) is suitable for intended purpose.

5. Test for ---b(4)---------- on MenW conjugate in DS ----b(4)----------

----b(4)----- ----------

Documents reviewed, SOP 202150-02, b(4) 07.021 VP1 Rev. 1, b(4) 07.021 VP2 Rev. 1, b(4) 07.021 VR1 Rev. 1, b(4) 07.021 VP2 Rev. 2 and b(4) 07.021 VR2 Rev. 2.

DPQ's Comment (Comment 1 in Information Request dated May 22, 2009)

----b(4)--- ----------

Novartis Response (Amendment 0.14)

----------*b(4)*--- ----------

-----*b(4)*---- --

DPQ's Review of Novartis Response

Validation protocol for quantitation of --b(4)------------------------can be similar as both these methods are --b(4)--------------- and would require evaluation of similar validation parameters. Novartis explanation to use a similar approach to validate a method for ----b(4)------------------------------ ---------------------- is acceptable.

Conclusion

The use of --b(4)-- of MenW-CRM conjugate (discussed in Section B.1 of this review memo) is acceptable. After addressing the method validation issues (discussed in Section A.3 of this review memo), the method used for --b(4)--- ------------------------------ ---------------------------- in MenW-CRM conjugate (DS) is suitable for intended purpose.

6. Test for --b(4)---------------------------------- on MenW conjugate in DP (--b(4)----------)

----b(4)---- ---

--- ----

-------b(4)---- ----------

Documents reviewed, SOP 202156-05, b(4) 07.029 VP1 Rev. 2, b(4) 07.029 VR1 Rev. 4

DPQ's Comment (Comment 3 in Information Request dated May 22, 2009)

----b(4)--- ----------

Novartis Response (Amendment 0.14)

Please consider that the document number for the SOP b(4) 07.029 is 202156 (and not 202150 as reported in the question). In addition, the revision provided in BLA for this SOP is 05 (and not 02 as reported in the question). Novartis apologizes if any narrative provided may have caused a misunderstanding.

The samples prepared for accuracy test were suitably --b(4)----------sample, in order to make --b(4)---------- fall within the calibration curve, and then treated as described in SOP b(4) 07.029 Rev. 5, (i.e., ----b(4)----------

Please note that revision 06 of SOP 202156, now valid, does not differ in the ----b(4)---------- from the revision 5, used in the validation study.

DPQ's Review of Novartis Response

The response is adequate.

Conclusion

The use of ----b(4)---------- of MenW-CRM conjugate (discussed in Section B.1 of this review memo) is acceptable. After addressing the method validation issues (discussed in Section A.3 of this review memo), the method used for ---b(4)---------- in MenW-CRM conjugate (DP) is suitable for intended purpose.

7. Test for ---b(4)------------------------------ on MenY conjugate in DS (-b(4)------)

---b(4)--- ---

Documents reviewed, SOP 202150-02, b(4) 07.021 VP2 Rev. 2 and b(4) 07.021 VR2 Rev. 2

Conclusion

The use of --b(4)-- of MenY-CRM conjugate (discussed in Section B.1 of this review memo) is acceptable. After addressing the method validation issues (discussed in Section A.3 of this review memo), the method used for --b(4)------------------------------------ ------------------- in MenY-CRM conjugate (DS) is suitable for intended purpose.

8. Test for ---b(4)---------------------------------- on MenY conjugate in DP (--b(4)------)

--b(4)---- ---

----b(4)----------

Documents reviewed, SOP 202156-05, b(4) 07.029 VP1 Rev. 2, b(4) 07.029 VR1 Rev. 4

Conclusion

The use of --b(4)---------- of MenY-CRM conjugate (discussed in Section B.1 of this review memo) is acceptable. Response discussed in Section B.6 of this review memo on spiking experiments in --b(4)---------- method is adequate. After addressing the method validation issues (discussed in Section A.3 of this review memo), the method used for --b(4)---------- in MenY-CRM conjugate (DP) is suitable for intended purpose.

9. Test for Protein Concentration (b(4)) on ----b(4)----------, MenA-CRM (DP), ----b(4)----------

--b(4)--------. To validate this method, precision (repeatability and intermediate precision), accuracy, specificity, linearity, range, and robustness for this assay were evaluated.

Documents reviewed, SOP 202671-09, b(4) 07.122 VP8 Rev.1 -b(4)---07.122 VR8 Rev. 3, b(4) 07.122 VP14 Rev. 4, b(4) 07.122 VR14 Rev. 4, b(4) 07.122 VP9 Rev. 4, b(4) 07.122 VR9 Rev. 4, b(4) 07.122 VP10 Rev. 5, b(4) 07.122 VR10 Rev. 5, b(4) 07.122 VR5 Rev. 1, b(4) 07.122 VP7 Rev. 3 and b(4) 07.122 VR7 Rev. 3

DPQ's Comment (Question 7d in the CR letter)

--b(4)---

Novartis Response (Amendment 0.15)

-----*b(4)*--- --

DPQ's Review of Novartis Response

--b(4)-- ---

---. The response is acceptable.

Conclusion

After addressing the method validation comment (Section A.3.b(i) of this review memo), the protein determination method is suitable for intended purposes.

10. --b(4)-- --- of CRM_{197} --b(4)-------- -- on MenA-CRM (DS), MenC-CRM (DS), MenW-CRM (DS), MenY-CRM (DS)

----b(4)--- ---

----b(4)--- ----------

----b(4)---- ----------

Documents reviewed, SOP 202621-07, b(4)07.216 VP3 Rev. 1, b(4) 07.216 VR3 Rev. 1, b(4) 07.216 VP2 Rev. 1, b(4) 07.216 VR2 Rev. 1, b(4) 07.216 VP4 Rev. 0, b(4) 07.216 VR4 Rev. 2, b(4) 07.216 VR4 Rev. 1, b(4) 07.216 VP1 Rev. 1, b(4) 07.216 VR1 Rev. 1.

Conclusion

After addressing the method validation comments (Section A.3 of this review memo), the method to --b(4)---------- and ---b(4)----of CRM_{197} --b(4)---------- for MenA-CRM (DS), MenC-CRM (DS), MenW-CRM (DS), MenY-CRM (DS) is suitable for intended purposes.

11. -b(4)-- Test for CRM_{197} on MenA-CRM (DS), MenC-CRM (DS), MenW-CRM (DS), MenY-CRM (DS)

--b(4)---- ----------

----b(4)---------- ----------

Documents reviewed, SOP 201700-03, b(4) 07.062 VP2 Rev. 0, b(4) 07.062 VR2 Rev. 0 **,** b(4) 07.062 VP4 Rev. 0, b(4) 07.062 VR4 Rev. 0

Conclusion

---b(4)---------- method to establish --b(4)----- of CRM_{197} is suitable for intended use.

12. -b(4)---------- Test on MenA-CRM (DS)

----b(4)--- ----------

Documents Reviewed, SOP 201717-03 (b(4) 07.209), b(4) 07.209 VP4 Rev. 0, b(4) 07.209 VR4 Rev. 0, b(4) 07.209 VP1 Rev. 0, b(4) 07.209 VR1 Rev. 1

Conclusion

After addressing the comments discussed in Section A.3.e of this review memo, -b(4)- to establish -b(4)- of MenA-CRM is suitable for intended use.

13. Identity Test for --b(4)---------- and MenCWY (DP)

---b(4)--- ----------

-

----b(4)--- ----------

Documents reviewed, SOP 201711-02 (b(4) 07.166), b(4) 07.166 VP6 Rev. 0, b(4) 07.166 VR6 Rev. 0, b(4) 07.166 VR3 Rev. 0, b(4) 07.166 VP3 Rev. 0, b(4) 07.166 VP4 Rev. 0, b(4) 07.166 VR4 Rev. 1, b(4) 07.166 VR4 Rev. 0 and b(4) 07-033 Rev. 0

Conclusion

After addressing the comments discussed in Section A.3.e of this review memo, --b(4)---------- to establish identity of MenC-CRM conjugate at -b(4)----- and DP stages is suitable for intended use.

14. ---b(4)---------- Test on MenW-CRM (DS)

----b(4)--- ----------

Documents reviewed, SOP 201717-03 (b(4) 07.209), b(4)07.209 VP6 Rev. 0, b(4) 07.209 VR6 Rev. 0, b(4) 07.209 VP3 Rev. 0 and b(4) 07.209 VR3 Rev. 1

Conclusion

After addressing the comments discussed in Section A.3.e of this review memo, -b(4)- to establish --b(4)---- of MenW-CRM conjugate is suitable for intended use.

15. --b(4)---------- Test on MenY-CRM (DS)

----b(4)---- ----------

-----b(4)---- --

Documents reviewed, SOP 201717-03 (b(4) 07.209), b(4) 07.209 VP5 Rev. 0, b(4) 07.209 VR5 Rev. 0 and b(4) 07.209 VP2 Rev. 0 and b(4) 07.209 VR2 Rev. 1

Conclusion

After addressing the comments discussed in Section A.3.e of this review memo, -b(4)--- to establish --b(4)---- of MenY-CRM conjugate is suitable for intended use.

16. Identity Test for MenA-CRM (DP)

The identification of MenA-CRM Conjugate is performed by ---b(4)------- ------------------------ The -b(4)-method uses a ----b(4)---- -------------------- --- --- --- --- --- --- --- --. For method validation, specificity and robustness were evaluated.

Documents reviewed, SOP 201715-03 (b(4) 07.190), b(4) 07.190 VP1 Rev. 1, b(4) 07.190 VR1 Rev. 1 and b(4) 04-037 Rev. 0

Conclusion

-b(4)--- to establish identity of MenA-CRM conjugate in DP is suitable for intended use.

17. Identity Test for MenW-CRM and MenY-CRM on MenCWY (DP)

The identification of MenW-CRM Conjugate and MenY-CRM Conjugate is performed by an ------b(4)--- method ------b(4)--

------b(4)------ ----------

For method validation, specificity and robustness were evaluated.

Documents reviewed, SOP 201715-03 (b(4) 07.190), b(4) 07.190 VP3 Rev. 0, b(4) 07.190 VR3 Rev. 0, b(4) 07.190 VP2 Rev. 1, b(4) 07.190 VR2 Rev. 0, b(4) 07.190 VR2 Rev. 1, b(4) 06-048 Rev. 1 and b(4) 08-054 Rev. 0.

Conclusion

After addressing the comments discussed in Section A.3.e of this review memo, --b(4)---------- to establish identities of MenW-CRM and MenY-CRM conjugates in Menveo CWY DP is suitable for intended use.

18. Test for --b(4)---------- on MenA-CRM (DS), MenC-CRM (DS), MenW-CRM (DS), MenY-CRM (DS)

----b(4)---- ----------

Documents reviewed, SOP 202781-05, b(4) 07.007 VP6 Rev. 0, b(4) 07.007 VR6 Rev. 0 and b(4) 07.007 QR2 Rev. 1, b(4) 07.007 VP 6 Rev. 1 and b(4) 07.007 VR 6 Rev. 1

DPQ's Comment (Question 7e (i) in the CR letter)

The following issues need to be addressed relating to the --b(4)---------- ---------- MenC, MenW, MenY and MenA, SOP 202781-05 (English translation 250043).

---b(4)--- ----------

---------b(4)--- --

Novartis Response (Amendment 0.15)

---*b(4)*-- ---

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

----b(4)---- ----------

DPQ's Review of Novartis Response

Novartis explanation for the --b(4)---------- and specification of -b(4)--- is acceptable.

DPQ's Comment (Question 7e (ii) in the CR letter)

----b(4)----- ----------

Novartis Response (Amendment 0.15)

---b(4)--- ----------

DPQ's Review of Novartis Response

Additional validation study performed to define LOD is adequate.

Conclusion

The method is suitable for intended use.

19. Test --b(4)---------- on MenA-CRM (DS), MenC-CRM (DS), MenW-CRM (DS), MenY-CRM (DS)

----b(4)---- ----------

Documents reviewed, SOP 226491-03, 226491 VP6 Rev. 2 and 226491 VR6 Rev. 2, 226491 VP7 Rev. 2 and 226491 VR7 Rev. 2, 226491 VP8 Rev. 2 and 226491 VR8 Rev. 2, 226491 VP5 Rev. 2 and 226491 VR5 Rev. 2.

Conclusion

After addressing method validation issues for the -b(4)--- (discussed in section A.3 of this review memo), the method is suitable for intended purposes.

20. --b(4)-------- Test for MenA-CRM (DS), MenC-CRM (DS), MenW-CRM (DS), MenY-CRM (DS)

----b(4)--- ----------

Documents reviewed, SOP 202289-11, b(4)07.117 VR25 Rev. 1, b(4) 07.117 VR25 Rev. 0, b(4) 07.117 VR106 Rev. 0, b(4) 07.117 VR55 Rev. 1, b(4) 07.117 VR55 Rev. 0, and b(4) 07.117 VR107 Rev. 0.

Conclusion

----b(4)-- ----------

----------. The method is suitable for intended purpose.

21. Endotoxin Test for ----b(4)----------, MenA Lyophilized (DP) and MenCWY Liquid (DP)

----b(4)--- ----------

Documents reviewed, SOP 201708-06, b(4) 07.149 VP1 Rev. 0, b(4)07.149 VR1 Rev. 0, b(4) 07.149 VR1 Rev. 1, b(4) 07.149 VP8 Rev. 0, b(4) 07.149 VR8 Rev. 1, b(4) 07.149 VP14 Rev. 2, b(4) 07.149 VR14 Rev. 2, b(4) 07.149 VP20 Rev. 1, b(4) 07.149 VR20 Rev. 1, b(4) 07.149 VP21 Rev. 1, b(4) 07.149 VR21 Rev. 1, b(4) 07.149 VP22 Rev. 1, b(4) 07.149 VR22 Rev. 1, b(4) 07.149 VP30 Rev. 1, b(4) 07.149 VR30 Rev. 1, b(4) 07.149 VP31 Rev. 1, b(4) 07.149 VR31 Rev. 1, b(4) 07.149 VP47 Rev. 0, b(4) 07.149 VR47 Rev. 0.

Conclusion

Endotoxin ---b(4)---------- ----------. The method is suitable for intended purpose.

22. Test for Residual Moisture on MenA Lyophilized (DP)

The test has been performed ----b(4)--- ----------

------b(4)--- --

Documents reviewed, SOP 202548-05, b(4) 07.009 QP3 Rev. 0 and b(4) 07.009 QR3 Rev. 0

Conclusion

The method is suitable for intended purpose.

23. Test for --b(4)------ on MenA Lyophilized (DP)

---b(4)--- ---

Documents reviewed, SOP 202590-06, b(4) 07.155 VP2 Rev. 0 and b(4) 07.155 VR2 Rev. 3

Conclusion

After addressing method validation issues for the -b(4)- test (discussed in section A.3 of this review memo), the method is suitable for intended purposes.

24. Sterility Test on MenA Lyophilized (DP) and MenCWY Liquid (DP)

The test is performed according to ---b(4)--- ------------------------------------
----

----b(4)--- ---

Documents reviewed, SOP 201631-22, b(4) 07.001 VR49 Rev. 0 and b(4) 07.001 VR53 Rev. 0

Conclusion

The test has been adequately verified for bacterostasis and fungistasis using appropriate sample matrices. The method is suitable for intended purpose.

25. General Safety/Abnormal Toxicity Test on DP

General Safety/Abnormal Toxicity test is conducted on the reconstituted vaccine (MenACWY Conjugate Vaccine). The test is performed according to -b(4)---------. The test consists of evaluating signs of illness in the animals treated with the vaccine. --b(4)- --- ---------------- The animals are weighed at day 0 (before injection) and day 7 (after injection) and observed each working day. The product passes if all animals survive and do not show any particular signs of illness. The final weight of each animal must be at least the same as the initial weight.

Document Review, SOP 201798-09, b(4) 07.068 VP4 Rev. 0 and b(4)07.068 VR4 Rev. 0

Conclusion

The method is consistent with 21 CFR 610.11 and suitable for intended purpose.

C. Other Methods on Polysaccharides

1. ---b(4)- --------------------------------

-----b(4)--- --

DPQ's Comment (Comment 4 in Information Request dated May 22, 2009)

----b(4)-- ---

Novartis Response Amendment 0.14)

----*b(4)*--- --

Conclusion

Novartis response is adequate. The method is suitable for intended purpose.