MEMORANDUM

Date: 17 November, 2014

From: Hsiaoling Wang, Ph.D.

CMC Reviewer

Laboratory of Analytical Chemistry and Blood Related Products (LACBRP)

Division of Biological Standards and Quality Control (DBSQC)

Office of Compliance and Biologics Quality (OCBQ)

Center for Biologics Evaluation and Research (CBER)

Food and Drug Administration (FDA)

To: **Biologics License Application Submission Tracking Number # 125546/0**

Subject: **Review of Analytical Procedures for Drug Substance of Biologics License Application for Meningococcal Group B Vaccine**

Through: Lokesh Bhattacharyya, Ph.D., Lab Chief, LACBRP/DBSQC/OCBQ/CBER

William M. McCormick, Ph.D., Director, DBSQC/OCBQ/CBER

Cc: Edward Wolfgang, MSA, Lead RPM, DVRPA/OVRR/CBER

Margret Bash, MD. MPH, Chair, BLA Review Committee, DBPAP/OVRR/CBER

Applicant: Novartis Vaccines and Diagnostics

Product: Bexsero - Meningococcal Group B Vaccine

Biologics License Application (BLA) Submission Tracking Number (STN) #: 125546

Submission received by CBER: July 03, 2014

Review completed: November 17, 2014

Material Reviewed
Method qualifications for:
1) ---(b)(4)----- determination for concentrated bulk of recombinant proteins rp287-953, rp961c and rp936-741 on the drug substance (DS)
2) ---(b)(4)----- test performed on DS outer membrane vehicle (OMV)
3) (b)(4) test performed on DS OMV
4) ---(b)(4)----- determination on DS OMV
5) --(b)(4)-- determination on DS OMV

Executive Summary:
After a thorough review of this BLA submission, this DBSQC reviewer finds that Novartis's ---(b)(4)---- assay for DS of recombinant protein bulks and (b)(4) test for DS OMV are qualified in accordance with ------------------(b)(4)-- assays are adequately validated for the intended use by evaluating methods with characteristics of specificity, ---(b)(4)-----, precision, linearity, range and robustness. In addition, this reviewer considers --(b)(4)-- test performed on DS OMV acceptable without method validation.

Novartis commits to re-assess the process capability and specification for the ---(b)(4)-------- of DS rp287-953 when more data is available.

Background
Novartis Meningococcal B Recombinant Vaccine Bexsero® is indicated for active immunization against invasive disease caused by N. meningitidis serogroup B strains in subjects 10 through 25 years of age.

The drug product is composed of four active ingredients:

1) Recombinant Protein (rp) 287-953: rp287-953 is a recombinant N. meningitidis serogroup B Neisserial Heparin Binding Antigen (NHBA) fusion protein. Protein 287 derived from strain NZ98/254 is fused with the accessory protein 953, which is derived from strain 2996.
2) Recombinant Protein (rp) 936-741: rp936-741 is a recombinant N. meningitidis serogroup B factor H binding protein (fHbp) fusion protein. Protein 741 derived from strain MC58 is fused with the accessory protein 936, which is derived from strain 2996.
3) Recombinant Protein (rp) 961c: rp961c is a fragment of N. meningitidis serogroup B Neisseria adhesin A (NadA) protein. It is derived from strain 2996.
4) Outer Membrane Vesicle (OMV): OMV is derived from N. meningitidis serogroup B strain NZ98/254 (a.k.a., PorA P1.4).

The Bexsero® vaccine contains 50 µg of each of the three purified recombinant protein antigens, with 25 µg of OMV measured as amount of total protein containing the PorA P1.4, and 1.5 mg of aluminum hydroxide per 0.5 ml dose. The excipients in a vaccine dose contain 10 mg sucrose, (b)(4) mg sodium chloride, 0.776 mg histidine, and water for injection.

The Division of Biological Standards and Quality Control (DBSQC) reviews BLA and related supplements to ensure analytical methods are adequately validated for the intended use.

Documents Reviewed
- 3.2.S.4.1 Specification
- 3.2.S.4.2 Analytical Procedures: ---(b)(4)------
- (b)(4) SOP 35.339: Calibrating --------(b)(4)--- Measurements ------------(b)(4)------------------------- or equivalent instrument)
- 3.2.S.4.3 Validation of Analytical Procedures: ---(b)(4)---------- [RP287-953]
- 3.2.S.4.4 Batch Analyses
- 3.2.S.4.5 Justification of Specification
- 3.2.S.4.2 Appearance
- Novartis SOP 202564-20: Evaluation of the ---(b)(4)----- of Lyophilized or Liquid Pharmaceutical Forms
- 3.2.S.4.2 Analytical Procedures (b)(4)
- Novartis SOP 202553-20: Measurement of (b)(4) with the ---(b)(4)-------- Method
- 3.2.S.4.3 Validation of Analytical Procedures (b)(4)
- 3.2.S.4.2 Analytical Procedures ---(b)(4)-----
- Novartis SOP 202612-09: Determination of the ---(b)(4)---------------------- in MEN B samples
- 3.2.S.4.3 Validation of Analytical Procedures Deoxycholate [OMV - Rosia]
- Validation report No. 315815-01: Validation Report of the method for ---(b)(4)------------------------------- in samples of Men B New Zealand in the phases of ---(b)(4)--(b)(4)---
- 3.2.S.4.2 Analytical Procedures (b)(4) [OMV -Rosia]
- Novartis SOP 202590-16: Determination of ----(b)(4)------------------ Method
- 3.2.S.4.3 Validation of Analytical Procedures (b)(4)-- [OMV - Rosia]
- Validation report No.314640-03: Validation Report of the method for (b)(4) determination in samples of Men B New Zealand in the phases of --(b)(4)--------------------------------
- 1.11.1 Information Amendment in STN 125546/0.14 (dated Sep. 26, 2014)
- Validation report No. 315815-02: Validation Report of the method for ---(b)(4)--------------- determination in samples of Men B New Zealand in the phases of Filtered --(b)(4)--
- 1.11.1 Information Amendment in STN 125546/0.23 (dated Oct. 31, 2014)
- 1.11.1 Information Amendment in STN 125546/0.24 (dated Nov. 7, 2014)

Review

1. ----(b)(4)------ **for all three ----(b)(4)------------- of recombinant proteins**

<u>Method</u>
Aliquots of the ----------(b)(4)------ of rp287-953, rp961c and rp936-741 are tested for ---(b)(4)----- by a -----(b)(4)--------- according to the ----(b)(4)-------- method described in ------
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---------------------------------(b)(4)---

--------------. The current specifications are --------------------(b)(4)----------------------------------
---------------------------- respectively. All results are within the specification limits.

<u>Method Validation</u>
The sponsor has not performed method validation because this is a ---(b)(4)--- method. This is acceptable.

<u>Information Request (IR) and reviews</u>
An IR regarding this assay was sent to the sponsor on September 12, 2014. The response was included in amendment 14 (dated Sep. 26, 2014).

Please provide rationale of ---(b)(4)------ specifications for rp287-953 and rp936-741 protein --------(b)(4)------. The summary of historical ---(b)(4)------ data from 2007 to 2010 of the --------(b)(4)---------- and specifications of them are both listed in Table 1. All these data are extracted from submitted 3.2.S.4.5 "Justification of Specification".

[(b)(4)]

Sponsor's response:
The ----(b)(4)---- specification of the ---(b)(4)----------- for rp936-741 was established based on the following rationale: the ----(b)(4)---- specification range of the -----(b)(4)--------------------- ------------------ was aligned to the ----(b)(4)---- specification range ----(b)(4)------------ of the buffer used in the ----------(b)(4)------------- operation of the purification process.
The function of this step is to ----(b)(4)------------- from the previous ----(b)(4)------- step in to the ------------(b)(4)-- specification for this ------------(b)(4)

(b)(4) protein is designed to demonstrate that the protein has been ----(b)(4)------ during the
------(b)(4)------------------ step of the ---(b)(4)----- process into the required formulation buffer
for the product (drug substance).

The ----(b)(4)--- specification of the ----(b)(4)-------- for rp287-953 was established based on
the following rationale: the ----(b)(4)---- specification range for the -----------(b)(4)------------
----------------- is set on the basis of the average -------(b)(4)--------------------- measurements
from (b)(4) batches of drug substances generated during development at pilot scale in Novartis
(b)(4) and ---(b)(4)--------.

Review of the response:
The rationales of setting the ----(b)(4)---- specifications are provided. This reviewer thinks the
specification of DS (b)(4) should rely on ----(b)(4)---- measurements performed on ---(b)(4)---
lots at manufacturing scale. Besides results of (b)(4) lot samples are not statistically significant to
estimate the variation of process capability.

Dr. Cipollo, CMC Reviewer, OVRR, also does not agree with sponsor's explanation for
following reasons:
   1) The specification of rp936-741 is based on a step prior to the ---(b)(4)--------- stage
      where the test is used. Thus the current specification is not representative of its
      manufacturing experience.
   2) The specification was actually set using (b)(4) pilot scale lots for rp287-953. We do not
      concur with the use of pilot scale lots for the setting of this release specification.

The sponsor was asked to revise the specification to reflect historical performance of the
----(b)(4)----------- for rp936-741 and submit manufacturing scale lot data supporting
specifications reflecting historical performance of rp287-953 in the IR sent out Oct. 08, 2014.

The response to the IR of Oct. 08, 2014 was received in the amendment 23 on Oct. 31, 2014.
Data from ----(b)(4)-------- DS batches of rp936-741 released was used to calculate "average $\pm$
3σ" value of ----(b)(4)-------------------. The results adequately justified the proposed
specification: ----(b)(4)---------.

Data from (b)(4) commercial DS batches of rp287-953 released shows the "average $\pm 3\sigma$" to be
----(b)(4)--------------------. This relatively small dataset is considered by the sponsor as
insufficient to precisely evaluate the process capability and to estimate specification limits. The
sponsor has committed to re-assess the process capability and specification once a sufficient
dataset becomes available. A follow-up IR was sent to PRM on Nov. 10, 2014 to get timeline
of this reassessment as follow.

In the amendment 23 (dated Oct. 31, 2014), you stated "As such the company intends to re-assess the process capability and specification once a sufficiently dataset, including the 2014 production campaigns, becomes available. Following reassessment, the ---(b)(4)------ specification for rp287-953 drug substance will be updated accordingly and implemented in the next rp287-953 drug substance manufacturing campaign." in page 74 of 75. Please provide the timeline of your data reassessment and submission.

2. ---(b)(4)------ for outer membrane vehicle (OMV)

Method

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

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The specification is stated that the liquid must be --------------------(b)(4)--------------------------
---. All results in batch analysis met specification.

Method Validation
The method was not validated and no justification has been given for not validating. But as a simple visual inspection, not validating the method is acceptable.

The method is acceptable for the intended use.

3. (b)(4) determination for OMV

Method
(b)(4) of the OMV ----(b)(4)-------- is measured ------(b)(4)-------------- as per the procedure described in -----------(b)(4)--.

The (b)(4) assay is based on the measurement of the --

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

---.

Method Validation
A full validation is not performed because the test method complied with ------------(b)(4)-------
---------------. A sample qualification is performed based on sponsors' quality manual and best

practices. Intermediate precision was evaluated by -----(b)(4)---------------- between ------------
---(b)(4)-------------- after samples were removed from ---------------(b)(4)------------------------
-- lots of OMV ---(b)(4)------- samples. The combined
RSD values were ---(b)(4)---------- respectively, which meet the acceptance criterion of (b)(4).

The assay is approvable for (b)(4) measurement of OMV (b)(4).

4. ----------(b)(4)---------------------- for OMV

<u>Method</u>
The (b)(4) specification of OMV ----------(b)(4)------------------------------- of protein.

The amount of residual (b)(4) is determined ---------------------(b)(4)-----------------------------
-------------------. The principle of the method is based on an --
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--(b)(4)--

<u>Method Validation</u>
This quantitative method for an impurity is validated by evaluating the characteristics of
specificity, accuracy, precision, linearity, range and robustness.

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

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Linearity is demonstrated by both standard solutions between ---(b)(4)-------- and OMV (b)(4)
samples of one batch at different dilutions ---(b)(4)---------- each concentration level analyzed -

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

--(b)(4)--

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

The robustness of the assay is assessed by extending the -----------(b)(4)------------------------
for standard solutions and samples after the completion of the reaction. The variation of the
(b)(4) content in sample is only (b)(4) compared to the readings made in (b)(4).

Information Request (IR) and Reviews
An IR was sent to the sponsor on September 12, 2014. The responses were received on
September 26, 2014 (amendment 0.14).

For your validation report ((b)(4) No.315815-01) of this method,
  a) Please provide the linearity of the standard curve (page 13 of 23) as response
     (--(b)(4)--------------) versus (b)(4) concentration.

  b) We checked and found that the results of CV% in Table 10 are incorrect. Please
     recalculate and submit for review.

  c) We consider that validated range of linearity is between ---(b)(4)----- because the
     concentrations of ----(b)(4)---------- µg/ml are out of the range of the standard
     (calibration) curve.

d) Please provide the conversion from this validated range of linearity in the unit of µg/ml to the (b)(4) specification unit of µg/µg of protein (reportable value). We could not understand if your linear range encompasses the range of the proposed specification.

Sponsor's responses:

a) The Company acknowledges that the linearity curve shown in figure 1 on page 13 of validation report (-(b)(4)- No.315815-01) is labelled incorrectly. A verification of the raw data has been conducted and submitted. The validation report ((b)(4) No.315815-02) has been revised to provide the correct figure of the linearity plot.

b) The Company acknowledges that table 10 on page 15 of validation report ((b)(4) No.315815-01) shows incorrect %CV values. A verification of the raw data and a re-calculation of the results reported in Table 10 of the updated validation report (b)(4) No.315815-02.

c) The Company acknowledges the assessors comment regarding sample linearity but wishes to clarify the following points:

The validated range has been established as the interval between the upper and lower concentration of the analyte in the sample for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy and linearity (in accordance with ICH guidance). Data obtained during validation indicates that the validated range is from ----(b)(4)---------.

According to the test method (SOP 202612), the working range is set between ----------(b)(4)----. It is important to highlight that routine test samples are diluted so that they fall within the middle of the range of the ---(b)(4)----- calibration curve ------------(b)(4)-------.

d) The specification for protein content is ---(b)(4)------------ whereas the ----(b)(4)-------------------- specification is ----(b)(4)------ of protein. Therefore the theoretical range of ---(b)(4)------- concentrations are between ------------(b)(4)----------------------------------.

The Company would like to clarify that test samples are normally diluted so that they fall within the middle of the range of the ---(b)(4)------ calibration curve. The dilution factor applied is used to calculate actual levels of ---(b)(4)------- present in the sample.

Review of the responses:

a) The provided linear curve is satisfactory with a correlation coefficient value of ---(b)(4)----.

b) The response is satisfactory.

    c) We don't agree with the sponsor explanation because the submitted data does not support the linear range of ---(b)(4)---------. A follow-up IR was sent to the sponsor to have a correct range for the assay.

    d) The response is acceptable.

A follow-up IR was communicated to the sponsor on Oct. 23, 2014 as follow:

Precision results in Table 10 of the validation report (315815-02) show that the result at -----(b)(4)- did not meet acceptance criterion of (b)(4). Therefore, this concentration cannot be part of the validated linear range of the assay. In addition, as we pointed out in the Sep. 12, 2014 IR that "the sample with concentration of ---(b)(4)------ is out of the range of the standard (calibration) curve" in the Table 10 of the validation report (315815-02) because calibration range is between ---(b)(4)---------. Based on the results you submitted, your validated linear range is ----(b)(4)-------. Please revise the linear range of your assay and submit for review. Alternately, please provide adequate data in support of the proposed linear range of ---(b)(4)-------.

The response was received on November 7, 2014 in the amendment 0.24. The sponsor stated "*The Company acknowledges the concerns with regards to the linear range. The accepted range will be ------(b)(4)---------------------. Re-validation of the analytical method will be reported by use of the annual report procedure.*"

In conclusion, this method is adequately validated for the intended use.

5. (b)(4) content for OMV

Method
The determination of -(b)(4)- is based on a ---(b)(4)---- reaction. ---(b)(4)---- in (b)(4) environment reacts with the ---------------(b)(4)------------------------------ and results in a ---------(b)(4)--------------------- product. The amount of product is measured -------------(b)(4)--, which is proportional to the concentration of -(b)(4)-. The concentration of -(b)(4)- in a sample is calculated from a calibration curve using a -(b)(4)- reference standard -----(b)(4)-------------.

The specification for -(b)(4)- of OMV is ---(b)(4)--.

Method Validation
This quantitative method is validated by evaluating the characteristics of specificity, accuracy, precision, linearity, range and robustness.

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

The robustness of the assay is assessed by testing the stability of reagents and the influence of ----------(b)(4)------------------------------. The results showed that ---(b)(4)---- is stable for (b)(4) days and -(b)(4) is stable for (b)(4) days concluding from --------------------(b)(4)---------------- ----------------. With the variation either ------------(b)(4)--- bath, the ------------(b)(4)------- generated absolute error of ------(b)(4)---------, respectively.

Information Request (IR) and review
An IR was sent to the sponsor on September 12, 2014. The responses were received on September 26, 2014 in the amendment 0.14.

For your validation report ((b)(4) No.314640-03) of this method,
   a) Validated range of linearity should be based on the linearity, accuracy and precision of the samples. The validated range from page 13 of the validation report is between ----------------(b)(4)------- because -------(b)(4)------------------------ are out of calibrated range. We also noticed that the validated range doesn't cover the specification of (b)(4), which is (b)(4)--. Please provide the validated range 80-120% of the specification range with supporting data.

   b) We found that the slope ratio of DS (b)(4) samples to standard solutions is (b)(4). The acceptable value is usually (b)(4). Your results suggest that using standard solutions as calibration model for (b)(4)- measurement of the DS sample is not appropriate. Please justify your decision of using such calibration model in the assay.

Sponsor's response:
   a) The validated range has been established as the interval between the upper and lower concentration of the analyte in the sample for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy and linearity. Data obtained during validation of the assay indicates that the validated range is from ------------(b)(4)---------.

      According to test method SOP 202590, the working range is set between ----(b)(4)------ ---------------. It is important to highlight that routine test samples are diluted to fall within the middle of the range of the (b)(4) calibration curve ---(b)(4)--------. The calibration range of -----(b)(4)-------- equates to a -(b)(4)- content of ---(b)(4)-- w/v, calculated according to method SOP 202590. The calculation accounts for the approximate 400 fold dilution applied to each sample prior to analysis.
      The (b)(4) specification is (b)(4)--; therefore -(b)(4)-- of the specification range is (b)(4), corresponding to ----------(b)(4)----------- which is within the validated and working range.

b) The Company justifies the continued use of the current calibration model based on the following points:

1) The slope ratio of 0.83 corresponds to a slope of 0.0024 for the drug substance bulk sample linearity and a slope of 0.0029 for the standard solution linearity. However it should be noted that other slope values obtained for standard curve linearity during method validation and subsequent routine testing (data shown below for 30 representative tests) are consistently less than 0.0029, as illustrated in Figure 1. As such the slope ratio of drug substance bulk samples to standard solutions using the data from figure 1 are consistently greater than or equal to 0.9.
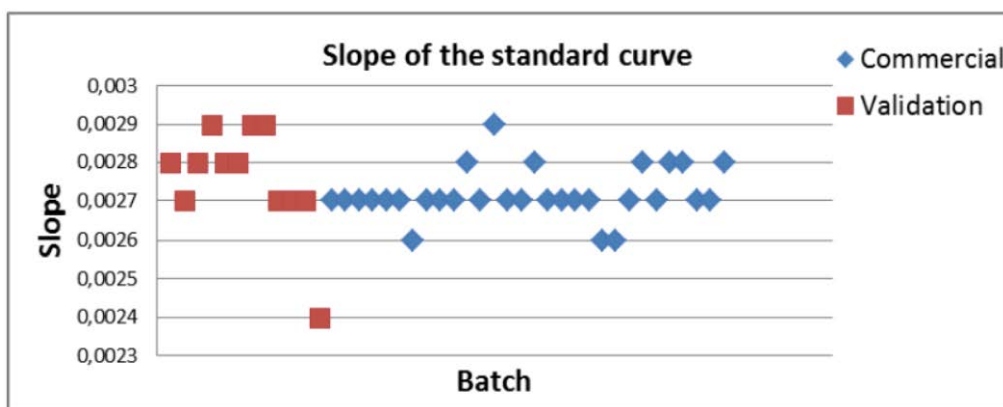

Figure 1. Comparison of Standard Curve Data

2) All the results obtained for recovery during the accuracy test ranged between 102% and 105%, providing additional confirmation that an underestimation of the sample does not occur during the test.

3) Results obtained from the assessment of specificity show that interference was not observed from either a synthetic sample matrix solution diluted 400 fold in water or a treated sample in which (b)(4) had been removed prior to analysis.

4) A qualified and independent positive control ---(b)(4)--------------------- is analyzed in each analytical session and this has to be within a predefined qualified range. This is one of the acceptance criteria for the test.

Review of the response:
a) Based on the provided supporting data, the validated linear range for this assay is -------
---(b)(4)------ rather than ---(b)(4)-------. That is equivalent to ---(b)(4)------ (w/v) which covers 80-120% of the specification of (b)(4).

b) The sponsor has provided following sufficient assurance for precision and accuracy of this assay:

1) The slopes of standard curves were consistently between 0.9-1.1 in their routine testing.
2) Recovery of accuracy study in the validated report is 102-105%, which meet the acceptance criterion of ---(b)(4)----.
3) There was no interference from either a synthetic matrix or a sample of placebo.
4) A qualified and independent positive control is used as system suitability check in the SOP.

In conclusion, the assay is adequately validated for the intended use.