Complete Review of Product CMC for BLA STN 125300, January 12, 2010 - Menveo

Date: 12 January 2010
To: File 125300
Through: Willie F. Vann, Ph.D., Lab Chief LBP, Chair File 125300
From: Darón I. Freedberg, Ph.D.
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SUBJECT: Complete Review of Product CMC for BLA STN 125300 - Meningococcal (Groups A, C, W-135 and Y) Oligosaccharide CRM197 Conjugate Vaccine (Menveo®) manufactured by Novartis

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Section 2.2- CTD Introduction;
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MenCWY liquid and MenA Lyo
Section 2.3.P.1- Description and composition of the Drug Product; **Section 2.3.P.2**-Pharmaceutical development; **Section 2.3.P.3**- Manufacture; **Section 2.3.P.4**- Control of Excipients; **Section 2.3.P.5**- Control of Drug Product; **Section 2.3.P.6**- Reference Standards or Materials; **Section 2.3.P.8**- Stability; **Section 3.2.P.1**- Description and Composition of Drug Product; **Section 3.2.P.2**- Pharmaceutical development; **Section 3.2.P.3**- Manufacture; **Section 3.2.P.4**- Control of Excipient; **Section 3.2.P.5**- Control of Drug Product; **Section 3.2.P.6**- Reference standards or materials; **Section 3.2.P.8**-Stability.
Amendments
125300/1- Received 21 November 2008;
125300/3- Received 19 December 2008;
125300/4- Received 15 January 2009;
125300/8- Received 30 March 2009;
125300/10- Received 17 April 2009;
125300/12- Received 15 May 2009;
125300/13- Received 17 June 2009;
125300/15- Received 21 August 2009;
125300/16 – Received 8 October 2009
125300/19 – Received 15 January 2010

Executive Summary & Recommendation

In BLA 125300, Novartis Vaccines and Diagnostics, Inc. requests a license for **Meningococcal (Groups A, C, Y and W-135) Oligosaccharide Diphtheria CRM_{197} Conjugate Vaccine** (tradename Menveo®) for the prevention of disease caused by *Neisseria meningitidis* serogroups A, C, W-135 and Y.

Menveo® is to be administered to people ranging in age from 11-55 years old. There is a present study under IND to extend the age range to children under 11 years of age.

Menveo® consists of four drug substances, each composed of an oligosaccharide covalently attached to the CRM_{197} protein. These drug substances are Meningococcal group A oligosaccharide to *Corynebacterium diphtheriae* CRM_{197} protein (MenA-CRM Conjugate), Meningococcal group C oligosaccharide to *Corynebacterium diphtheriae* CRM_{197} protein (MenC-CRM Conjugate), Meningococcal group W-135 oligosaccharide to *Corynebacterium diphtheriae* CRM_{197} protein (MenW-CRM Conjugate), and Meningococcal group Y oligosaccharide to *Corynebacterium diphtheriae* CRM_{197} protein (MenY-CRM Conjugate). Each drug substance is prepared from materials purified from two starting products of bacterial fermentation origin: *Corynebacterium diphtheriae* Cross Reactive Material 197 (CRM_{197}) and capsular polysaccharide (A, C, W-135 and Y obtained from *Neisseria meningitidis* serogroups A, C, W-135 and Y, respectively). There are a total of ----b(4)----------

Issues found in this application are summarized here and described in greater detail later in the review section. The major issues with this file were:

- stability testing of product intermediates;
- drug product dating period;
- characterization of process intermediates;
- discontinuing of important tests; and
- adequacy of routine testing procedures.

a) *Stability testing of process intermediates*

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

[b(4)]

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

[b(4)]

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

[b(4)]

Novartis requested a shelf life of 24 months for the drug product in the original submission. Subsequently, the request was revised to a 36 months shelf life. This request for a 36 month shelf life along with supporting data was submitted 25 November 2009 in amendment STN125300/0017.

[b(4)]

b). *Drug Product Dating period*

In the original submission (July 2008), Novartis had data that would only support a shelf-life of ---b(4)---------- for the MenCWY Drug Product. This deficiency was communicated in the CR letter (comment #3). In amendment 17, submitted on 25 November 2009, Novartis submitted data to support a --b(4)----- shelf-life for the process intermediate (see below).

Novartis has an ongoing stability study for -b(4)-. dating period for the MenA-CRM_{197} lyophilized powder. Novartis included stability data (section 3.2.P.8.3, pp. 7-26) for:

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

Novartis also has an ongoing stability study to support a --b(4)--- dating period for the MenA-CRM197 component. The current data in this study support an expiry of 36 months at 2° to 8° C, thus a 36 month dating is recommended by CBER for the MenA-CRM_{197} lyophilized powder. ---b(4)----------. ---b(4)----------

Drug Product	Original data support shelf-life @ b(4)	New data support Shelf life @ b(4)
MenA Lyo	**b(4)**	36 mos.
MenCWY Liquid	**b(4)**	36 mos.

During process development, several lots were used to demonstrate stability of MenCWYLiquid. Stability studies were done by Novartis to:

- define the shelf-life of MenCWY Liquid considering that the shelf-life is calculated starting from the formulation date
- confirm the container suitability considering that the MenCWY Liquid has been stored in the final container (--b(4)-- vial)

Novartis defines the date of manufacturing for MenCWY Liquid as the date of initiation of formulation. The proposed shelf-life for MenCWY Liquid, based on the CBER review team's evaluation of data available to date, is 36 months from the date of manufacture filled in vials ----b(4)----when stored a 2 to 8°C.

The firm submitted 12 month (--b(4)----------) and 24 month (---b(4)----------) stability data at 2-8 °C --b(4)---------- (5 mg dose). This information can be found in **section 3.2.P.8.3** in the original submission.

---b(4)---------- (pp. 21 – 30).

In the stability protocol the test for sterility is performed at zero time and not again until the 24 month time point. Additional data was requested in the Complete Response letter dated 25 June 2009.

"Please establish and provide data to support time limits for all critical manufacturing steps for Menveo." (comment # 1b taken from the CR letter)

The file now contains data through the 24 month time points for drug product in vials. In addition, data were submitted (November 2009) to support a 24 month dating period (Lots --b(4)----------). ---------- --b(4)----------). The data are in section **3.2.P.8.3**, **pp. 12- 24**.

The submission now contains stability data to support a 36 month dating period from date of manufacture, in response to a CR letter sent on 25 June 2009.

c).*Characterization of product intermediates*

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

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

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

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

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

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e). *adequacy of routine testing procedures*

In this area, CBER questioned some of the routine testing procedures and specifications set for Menveo®. Ten such issues were raised with respect to this in the CR letter (five in comment #5 and five in comment #7). We are approving a ---------b(4)--------specification of NMT b(4) for Men-CWY and NMT b(4) at release and NMT b(4) for stability for both Men-CWY and MenA-Lyo.

- **Specification for --b(4)--------------- in process intermediates** – CBER noted that the percent --b(4)------------ for MenA-CRM$_{197}$ conjugate does not match the corresponding value in the MenC, MenW-135 and MenY conjugates. CBER also commented that ---b(4)----------------- was too high and that the --b(4)--------- should be reduced to -b(4)----
  - Novartis responded that the final vaccine formulation contains twice as much MenA-CRM197 conjugate as the other conjugates in the formulation.
  - Novartis notes that the amount of MenC-CRM197 in the final formulation is calculated ---b(4)--- In the CR letter (comment # 4) CBER requested that Novartis reinstate a test for ----b(4)--
- **Specification for --b(4)----------- in drug product** - The data in the original submission justified --b(4)------------------------ and the specifications should be revised to reflect this.
  - In response to this comment, Novartis first responded that there have not been enough lots produced to confidently lower the amount of --b(4)-------in their release specifications. Nevertheless, they adjusted release specifications so that they could account for the percentage of -------b(4)-------. The sponsor has had enough experience

to know that a worst case scenario for increasing the --b(4)------- is about --b(4)----- As such, Novartis proposes to lower their release specification to the following:

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

	MenC-CRM	**MenW-CRM**	**MenY-CRM**	**MenA-CRM**
Release Specifications	b(4)	b(4)	b(4)	b(4)
Stability Specifications	b(4)	b(4)	b(4)	b(4)

- Protein concentration specifications – The specifications for the drug product, Menveo®, and MenA-Lyo were very broad (--b(4)----------). The liquid portion of the vaccine containing MenCWY conjugates had no protein concentration specification set. CBER suggested narrowing the MenA-Lyo specification range and asked for specifications for MenCWY liquid.
  - Novartis responded to this by explaining that the total protein specification depends on the ---b(4)----------
  - CBER will be approving the specification of -b(4)----- protein per vial of MenA-Lyo, as proposed by Novartis. The MenCWY will have no protein specification. As Novartis claims, they --b(4)---------- The protein concentration is only reported. I believe this reply is adequate and can be accepted, but I would like see a smaller range after Novartis has more experience with their production.
- Endotoxin specification - Submitted data did not support the specifications for endotoxin.
  - The upper limit of the endotoxin limit is a ---b(4)---------- While Novartis is aware that their specification can be lower, they note that an upper limit of -b(4)------- is acceptable in the EU. I agree that the current specification for endotoxin is adequate.
- CRM_{197} purity - Based on data in the BLA, CRM_{197} should be -b(4)-- pure; however, the specifications were set at -b(4)- purity. CBER asked Novartis to justify this specification or change it to the former as it is supported by the data.
  - Novartis provided more data to demonstrate that the lowest level of purity is-b(4)-and proposes to introduce an action limit of -b(4)- However, they plan to maintain their specification at -b(4)- I do not concur with this proposal. There is only one lot for which Novartis demonstrates -b(4)- purity; the rest are purer than -b(4)- Nevertheless, CBER will be approving -b(4)- purity with an alert level in case the purity should be -b(4)-
- **Inconsistency in calculating --b(4)----------** - CBER noted two procedures for calculating ---b(4)----------. One procedure is used to calculate the --b(4)---------- for MenW-135 and MenY (SOP 202606) and the second procedure is used for MenC (SOP 202628).
  - Novartis explained that MenC-CRM_{197} was in use in a different vaccine (Menjugate) that has been manufactured since 1998. Therefore, the assay is different from the other conjugates.

- To clarify, there is a different assay for the MenA oligosaccharide, but we would expect a different assay since MenA contains no --b(4)------, whereas the other three polysaccharides, MenC, MenW-135 and MenY all contain --b(4)--------
- **Discrepancy between quantitative determination of ---b(4)---------- in MenA-CRM_{197} and the corresponding determination for the MenC- CRM_{197}, MenW-CRM_{197} and MenY- CRM_{197}.** The procedure for determining --b(4)---------- in the MenA - CRM_{197} conjugate uses the --b(4)---------- as a standard. The procedure for the remaining Meningococcal polysaccharide - CRM_{197} conjugates utilizes the --b(4)----------.
- ----b(4)----------

- **Inconsistent methods used to characterize the different conjugates.** Quantitative methods used to determine --b(4)---------- in MenA - CRM_{197} and MenC - CRM_{197} use a -b(4)----, while those for MenW - CRM_{197} and MenY - CRM_{197} use --b(4)--------
- Novartis acknowledges this difference, which was in place because these --b(4)---------- were used in the past. Novartis notes that --b(4)---------- are now available and will switch over to the --b(4)---------- for the MenA-CRM_{197} and MenC-CRM_{197} conjugates.
- **Ambiguity in method used to determine protein concentration.** Two methods are described for quantifying ---------- -b(4)----------. The sponsor was not clear about which method they would use to quantify protein concentration.
- Novartis responds that they plan to continue to use both assays. The --b(4)--------- is used for historical reasons while the --b(4)------- was developed later. Since both methods have been used to -b(4)----------, Novartis plans to continue both assays for consistency purposes. Both assays will be used to measure protein concentrations. -b(4)- will be used to determine protein concentrations in the MenA-Lyo, ---b(4)----------.

  I recommend that BLA 125300 for Menveo® should be approved. I also recommend that Novartis reduce the specification for the amount of residual endotoxin in the final container. My review, which highlights the aspects I examined, is below.

REVIEW

Product Description

The vaccine consists of 10µg of a lyophilized powder of the Mening A conjugate and 5µg each of the Mening C, Y and W-135 oligosaccharide conjugates dissolved in water without an adjuvant. The dose is 0.5mL after reconstitution.

Drug Substance

The vaccine contains:

- *Neisseria meningitidis* serogroup A oligosaccharide-CRM_{197} conjugate;
- *Neisseria meningitidis* serogroup C oligosaccharide-CRM_{197} conjugate;

- *Neisseria meningitidis* serogroup W-135-oligosaccharide CRM_{197} conjugate; and
- *Neisseria meningitidis* serogroup Y oligosaccharide-CRM_{197} conjugate.

Process Intermediates – The major starting materials for the manufacture of the vaccines are listed below:

- *Neisseria meningitidis* serogroup A polysaccharide
- *Neisseria meningitidis* serogroup C polysaccharide;
- *Neisseria meningitidis* serogroup W-135 polysaccharide;
- *Neisseria meningitidis* serogroup Y polysaccharide; and
- *Corynebacterium diphtheriae* CRM_{197}.

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

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

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

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

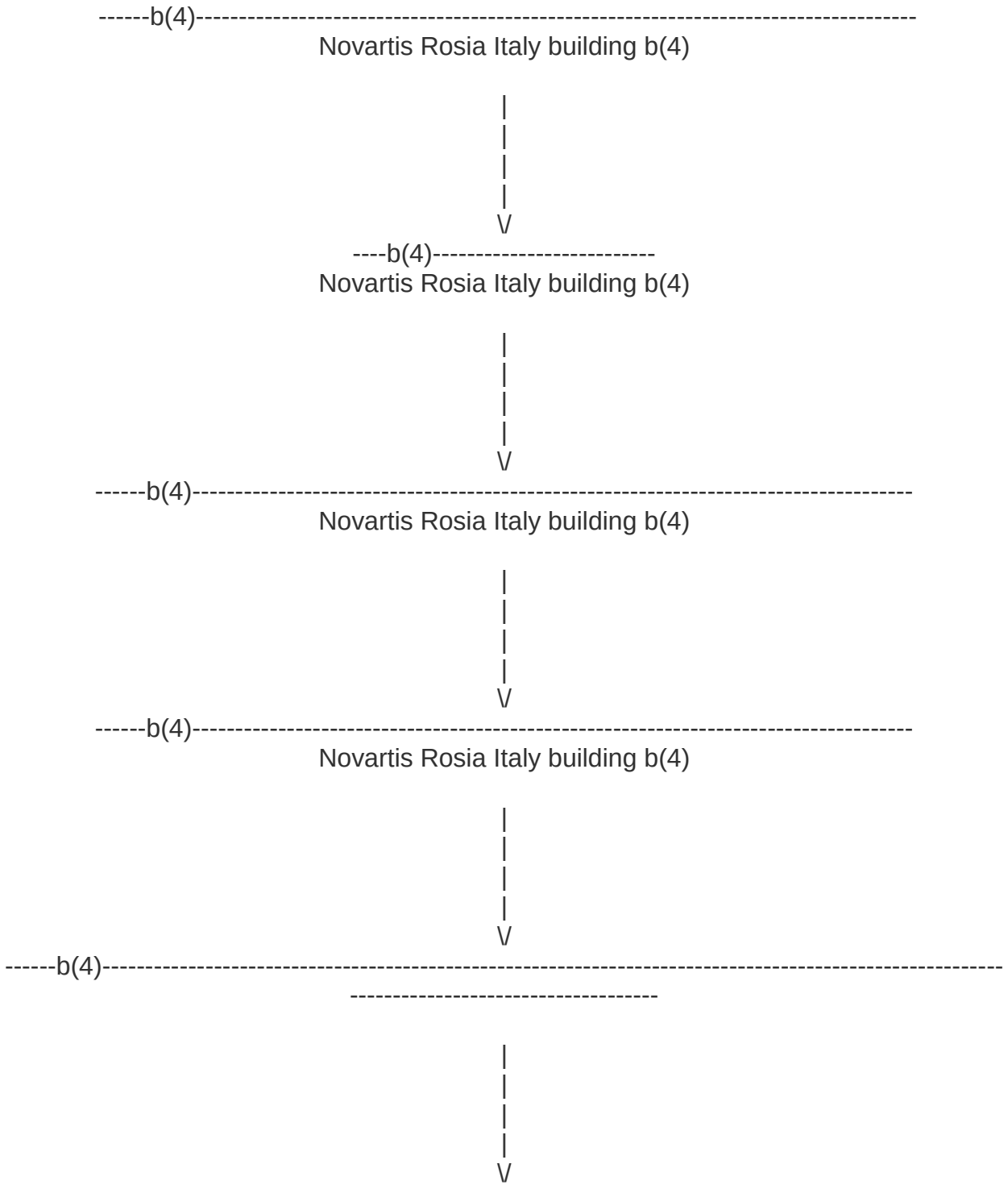
Manufacturing of drug product

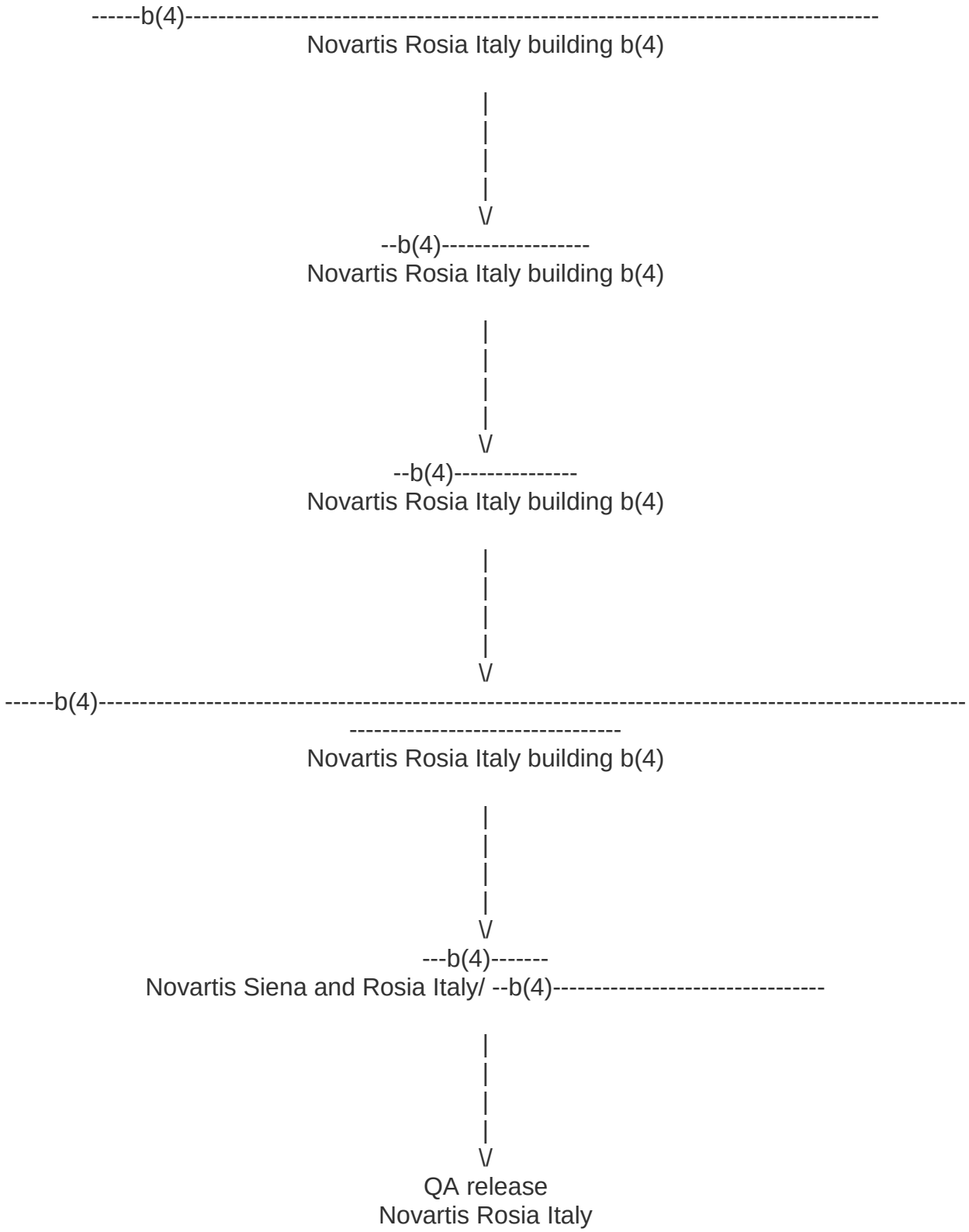
Novartis Meningococcal ACWY Conjugate Vaccine [MenACWY] vaccine is presented in two package forms:

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

- a multiple dose package consisting of 5 vials containing the MenA Lyo and 5 vials containing the MenCWY Liquid The contents of the vial MenA Lyo are reconstituted with the contents of --b(4)---------- or vial MenCWY Liquid in order to administer 0.5 mL of reconstituted vaccine (MenACWY).
The vaccine is administered after reconstitution. The final product is preservative-free and non-adjuvanted.

Overview of Operations and Facilities for Menveo Manufacturing





Return to TOC

Stability of the Drug Product –

Stability of Drug Product

During process development, several lots were used to prove stability of MenCWYLiquid. Completed tables with all available data are were reviewed. All the studies have been conducted to:

- define the shelf-life of MenCWY Liquid considering that the shelf-life is calculated starting from the formulation date
- prove the container suitability considering that the MenCWY Liquid has been storedin the final container (----b(4)---- vial)

Novartis defines the date of manufacturing as the date of formulation. The proposed shelf-life for MenCWY Liquid, based on data available to date, is 36 months from the date of manufacture filled in vials ----b(4)---- when stored a 2 to 8°C. An example of the data to support the dating period is given in the table below;

[b(4)]

Similarly, stability studies have been carried out using MenA lyophilized conjugate component (hereafter referred to as MenA Lyo) lots manufactured at Novartis Vaccines and Diagnostics --b(4)----------. The proposed shelf life for MenA Lyo, based on data available to date, is 36 months from the date of formulation when stored at 2° to 8°C.

[b(4)]

Recommendation: The data support a dating period for the Meningococcal Serogroups C, Y, and W-135 liquid conjugate component of no more than 36 months from the date of formulation of the final bulk when stored at 2 °C to 8 °C. The data also supports a dating period for the lyophilized Meningococcal Serogroup A Oligosaccharide Diphtheria CRM_{197} conjugate component is no more than 36 months from the date of formulation of the final bulk when stored at 2 °C to 8 °C. The dating period for the co-packaged Meningococcal Serogroups C, Y, and W-135 liquid conjugate component and lyophilized Meningococcal Serogroup A Oligosaccharide Diphtheria CRM_{197} conjugate component shall be no more than 36 months or whichever component has the earliest expiration date when stored at 2 °C to 8 °C

Routine and ongoing stability program –

The dating period for the co-packaged Meningococcal Serogroups C, Y, and W-135 liquid conjugate component and lyophilized Meningococcal Serogroup A Oligosaccharide Diphtheria CRM_{197} conjugate component shall be no more than 36 months or whichever component has the earliest expiration date when stored at 2 °C to 8 °C.

Novartis has committed to place one commercial lot per year into their routine stability program using the current ongoing stability protocol.

Stability indicating assays –
The following assays were used to access the stability of the drug product. The selection of the test outlined below is satisfactory to this reviewer.
Appearance -Visual appearance is performed to verify product quality. The MenCWY Liquid is examined for clarity, color and the absence of foreign particles.

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

Sterility - Sterility is performed using the ----b(4)---------- ---------- ---------- ---------- Positive controls and negative controls are also run in the assay. The lot meets the sterility test requirements ----b(4)----------.

Routine and ongoing stability program –
Novartis has committed to put one commercial lot per year into their routine stability program.
Novartis has committed to completing the stability protocol for MenCWY liquid conjugate component and MenA lyophilized conjugate component process validation lots through to the --b(4)------- shelf-life.

Stability of reconstituted product
A short-term stability study was performed to test the characteristics of the reconstituted vaccine after -b(4)---- of storage at --b(4)----------:

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

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

Issue 5:
b). *Drug Product Dating period*
Novartis submitted a request to extend the dating period from 24 months to 36 months for the final product.
In the original submission, Novartis had data to support a 24 month shelf-life for the final product. In the original application, Novartis requested that the product have an expiry date of 36 months, but only had data to support approval for 24 months. There were not enough data to support this request and this point was made in the CR letter, comment # 1. After receiving CBER's CR letter, Novartis requested to extend the final product's shelf life and revised it to the values listed below. To this end, they provided data to support this 36 month shelf-life.

[b(4)]

In addition to the above, Novartis requests a -b(4)-. dating period for the MenA-CRM197 lyophilized powder; there is no data to support this request (section 3.2.P.8.2). ---b(4)----

i. The requested dating period is now supported by stability data in the revised submission. In terms of increasing the shelf-life of the final product to 36 mos., I believe the data are adequate and support this dating period.

ii. The lyophilized MenA conjugate component of the vaccine should be dated based on available 36 month data. Extension of dating of this component should follow the standard policy of submitting a valid comparability protocol and sufficient data to support the extension of dating post licensure. Since the data were not provided, CBER cannot approve a ----b(4)----------

Issue 6:

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

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

Novartis agreed to reinstate the test, which acceptable to CBER. In addition, Novartis agreed to reinstate the formaldehyde test so that the level of formaldehyde can be reported on the label.

Issue 7:

e). *adequacy of routine testing procedures*

In this area, CBER questioned some of the routine testing procedures and specifications set for Menveo®. Ten such issues were raised with respect to this in the CR letter (five in question #5 and five in question #7).

- **Specification for --b(4)---------** – CBER noted that the --b(4)---------- for MenA-CRM_{197} conjugate does not match the corresponding value in the MenC, MenW-

135 and MenY conjugates. CBER also commented that ---b(4)---------- was too high and that the --b(4)---------- should be reduced to -b(4)-

- Novartis responded that the final vaccine formulation contains twice as much MenA-CRM_{197} conjugate as the other conjugates in the formulation.
- Novartis notes an important point that was brought up by CBER in the CR letter and is addressed in this memo. They note that the amount of MenC-CRM_{197} in the final formulation is calculated as --b(4)----------. This is important because it is ----b(4)----------.

I understand why the specifications are set differently for the MenA polysaccharide as compared with the others and I believe that Novartis' responses are adequate and acceptable.

Issue 8:

- **Specification for --b(4)---------** - The data in the original submission justified --b(4)---------- and the specifications should be revised to reflect this.
  - In response to this Novartis first commented that there have not been enough lots produced to confidently lower the amount of --b(4)---------- in their release specifications. Nevertheless, they adjusted release specifications so that they could account for the --b(4)----------. The sponsor has had enough experience to know that a worst case scenario for --b(4)---------- is about --b(4)---- As such, Novartis proposes to lower their release specification to the following:

	MenC-CRM	**MenW-CRM**	**MenY-CRM**	**MenA-CRM**
Release specification	b(4)	b(4)	b(4)	b(4)
Stability Specifications	b(4)	b(4)	b(4)	b(4)

The response is acceptable because these were the products with which Novartis conducted the clinical trials. However, I would have preferred a reduction in --b(4)----------

Issue 9:

- **Protein concentration specifications** – These specifications for the drug product, Menveo®, and MenA-Lyo were very broad (--b(4)----------). The liquid portion of the vaccine containing MenCWY liquid had no specification set for total protein. CBER suggested narrowing the range and asked for specifications for MenCWY liquid.
  - Novartis responded to this point by pointing out that the total protein specification depends on the ---b(4)---------- --------b(4)----------.

This response is expected, but highlights the potential for mis-formulation. It may be useful to revisit this issue after Novartis has more experience with these conjugate vaccines. If approved, the specifications would remain broad (-b(4)----- per vial).

Issue 10:

- **--b(4)---------**specification - Submitted data did not support the specifications for --b(4)----------

- The upper limit of the --b(4)------ limit is a --b(4)---------- While Novartis is aware that their specification can be lower, they note that an upper limit of --b(4)---------- is acceptable in the EU.
  I find this response lacking. Although the final --b(4)---------- concentration is acceptable in the EU and the USA, the total amount of --b(4)-------- can be quantified after the MenC-, MenY- and MenW- CRM_{197} conjugates are pooled. I believe that CBER should insist on a redefined specification. If approved, the --b(4)------- would be untested in the final vial and specifications would remain --b(4)----.

Issue 11:

- **CRM_{197} purity** - Based on data in the BLA, CRM_{197} should be -b(4)- pure; however, the specifications were set at -b(4)- purity. CBER asked Novartis to justify this specification or change it to the former as it is supported by the data.
  - Novartis provided more data to demonstrate that the lowest level of purity is b(4) and proposes to introduce an action limit of b(4) However, they plan to maintain their specification at b(4)
    It appears to me that only one lot had a b(4) purity level, otherwise, Novartis is consistently above b(4) I recommend that CBER insist that this specification is raised to b(4)If approved, the CRM_{197} could be only b(4) pure.

Issue 12:

- **Inconsistency in calculating ----b(4)----------** - CBER noted two procedures for calculating --b(4)----------. One procedure is used to calculate the --b(4)-------- for MenW-135 and MenY (SOP 202606), while a different procedure is used for MenC (SOP 202628).
  - Novartis explained that MenC-CRM_{197} was in use in a different vaccine (Menjugate) that has been manufactured since 1998. Therefore the assay is different from the other conjugates.
    This explanation is acceptable as is the continuation of the two assays. However, I would recommend that Novartis consolidate its methods in the future.

Issue 13:

- **Discrepancy between quantitative determination of --b(4)---------- in MenA-CRM_{197} and the corresponding determination for the MenC- CRM_{197}, MenW-CRM_{197} and MenY- CRM197.** The procedure for determining --b(4)---------- in the MenA - CRM_{197} conjugate uses the --b(4)---------- as a standard. The procedures for the remaining Meningococcal polysaccharide - CRM_{197} conjugates utilize the --b(4)----------.
  - ----b(4)----------
    Though this reply is difficult to understand because --b(4)---------- is commercially available. However, I do not consider this a problem and recommend that the test remain as Novartis suggests.

Issue 14:

- **Inconsistent methods used to characterize the different conjugates.** Quantitative methods used to determine --b(4)---------- in MenA - CRM_{197} and MenC - CRM197 use a -b(4)-----, while those for MenW - CRM_{197} and MenY - CRM_{197} use ---b(4)---------.

- Novartis acknowledges this difference, which was in place because these --b(4)-------- were used in the past. Novartis notes that --b(4)---------- are now available and will switch over to the -b(4)---------- for the MenA-CRM_{197} and MenC-CRM_{197} conjugates. This will be requested in a future supplement.
  I believe the response and the new action is acceptable.

Issue 15:

- **Ambiguity in method used to determine protein concentration.** Two methods are described for quantifying ---------- - --b(4)----------. The sponsor was not clear about which method they would use to quantify protein concentration.
- Novartis responds that they plan to continue to use both assays. The --b(4)-------- is used for historical reasons while the --b(4)------ was developed later. Since both methods have been used to --b(4)---------- Novartis plans to continue both assays for consistency purposes.
  This is understandable and acceptable. Only one assay is needed to pass, but the assays are used to make quality decisions. However, I would suggest that one method be used in the future to avoid confusion.