

Complete Review of CMC-Product of BLA STN 125300, February 2, 2010 - Menveo

DATE: February 2, 2010
FROM: Che-Hung Robert Lee, Ph.D., Laboratory of Bacterial Polysaccharides, HFM-428, Division of Bacterial, Parasitic, and Allergenic Products, OVRP
SUBJECT: Complete Review of CMC-Product of BLA STN 125300 Meningococcal (Groups A, C, W-135 and Y) Oligosaccharide CRM₁₉₇ Conjugate Vaccine, Menveo®, Novartis
TO: File, STN 125300
Cara Fiore, DVRPA, HFM-481
Willie Vann, Committee Chair, DBPAP
THROUGH: Willie Vann, Ph.D., Chief, Laboratory of Bacterial Polysaccharides, DBPAP

ITEMS REVIEWED

BLA 125300

- 2.3.S. CRM197
 - 2.3.S. MenA Polysaccharide
 - 2.3.S. MenC Polysaccharide
 - 2.3.S. MenW Polysaccharide
 - 2.3.S. MenY Polysaccharide
 - 2.3.S. MenA-CRM
 - 2.3.S. MenC-CRM
 - 2.3.S. MenW-CRM
 - 2.3.S. MenY-CRM
 - 2.3.P. MenCWY Liquid - Injection
 - 2.3.P. MenA Lyophilized - Injection
 - 2.3.S. CRM197
 - 3.2.S. MenA Polysaccharide
 - 3.2.S. MenC Polysaccharide
 - 3.2.S. MenW Polysaccharide
 - 3.2.S. MenY Polysaccharide
 - 3.2.S. MenA-CRM
 - 3.2.S. MenC-CRM
 - 3.2.S. MenW-CRM
 - 3.2.S. MenY-CRM
 - 3.2.P. MenCWY Liquid - Injection
 - 3.2.P. MenA Lyophilized - Injection
- Amendment 125300/0.3: Partial DI response
Amendment 125300/0.4: Partial DI response and additional information
Amendment 125300/0.5: Response to IRs

Amendment 125300/0.12: Stability Data for 24 months and packaging mock ups
Amendment 125300/0.13: Specifications and validation of specifications and manufacture data
Amendment 125300/0.15: Complete Response
Amendment 125300/0.17: Stability Data for 36 months, batch data for pre-licensure testing, PVP
Amendment 125300/0.19: Last minute BLA issues

- Response to CBER's Requests on Formaldehyde Testing and --b(4)----- Testing

SUMMARY

Novartis Vaccines and Diagnostics, Inc. is requesting licensure of Meningococcal (Groups A, C, W-135 and Y) Oligosaccharide CRM₁₉₇ Conjugate Vaccine (Menveo®). Menveo® is copackaged as a vial containing lyophilized MenA Conjugate Component and a vial ---b(4)-- containing the liquid MenCWY Conjugate Component. The selected final formulation contains 10-5-5-5 µg per oligosaccharide of *N. meningitides* serogroups A, C, W135 and Y, respectively, without adjuvant. The pharmaceutical form is a powder and a solvent for solution for injection. The dose is 0.5 mL (after reconstitution). Menveo® consists of four drug substances: Meningococcal group A oligosaccharide to *Corynebacterium diphtheriae* CRM₁₉₇ protein (MenA-CRM Conjugate), Meningococcal group C oligosaccharide to *Corynebacterium diphtheriae* CRM₁₉₇ protein (MenC-CRM Conjugate), Meningococcal group W-135 oligosaccharide to *Corynebacterium diphtheriae* CRM₁₉₇ protein (MenW-CRM Conjugate), and Meningococcal group Y oligosaccharide to *Corynebacterium diphtheriae* CRM₁₉₇ 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 (CRM₁₉₇) 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)-----

REVIEW

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

**5 Pages determined to be not releasable:
b(4)**

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

----- The proposed shelf life for MenA Lyo is 24 months when stored at 2-8 °C.
MenCWY Liquid (vial ----(b)(4)---) – The composition of MenCWY Liquid (vial or syringe) is MenC-CRM (5 µg MenC oligosaccharide, -b(4)----- CRM₁₉₇), MenW (5 µg MenW oligosaccharide, -b(4)---- CRM₁₉₇), MenY (5 µg MenY oligosaccharide, -b(4)----- CRM₁₉₇) in a ----b(4)-----

----- There are no overages in terms of content to account for loss or degradation. There is a b(4) overfill in the vials to allow the withdrawal and administration of 0.5 mL, after reconstitution of the lyophilized MenA Lyo with the MenCWY Liquid. --b(4)-----

----- The proposed shelf life for MenCWY Liquid is 24 months when stored at 2-8 °C.

COMMENTS

Global

1. All the specifications for the drug intermediates, drug substances and drug products are provisional. They need to be re-evaluated when enough lots have been produced. Please comment
2. -b(4)----- of each (MenA, C, W-135 and Y) polysaccharide, each conjugate, and Menveo® MenA Lyo needs to be included in their lot release specifications.
3. Please provide the SOP --b(4)----- determination of each (MenA, C, W-135 and Y) conjugate and Menveo® MenA Lyo.
4. Please clarify the storage temperature --b(4)----- for each (MenA, C, W-135 and Y) polysaccharide and each conjugate throughout the entire BLA submission.
5. **3.2.S.2.5 Process Validation and/or Evaluation, *MenA polysaccharide*, Page 15 of 29, Line 16; *MenC polysaccharide*, Page 18 of 33, Line 16; *MenW-135 polysaccharide*, Page 18 of 31, Line 11; *MenY polysaccharide*, Page 18 of 29, Line 11:** Please indicate that ----b(4)-----.
6. **3.2.S.2.5.Process Validation and/or Evaluation, *MenA-CRM Conjugate*, Page 24 of 46, Lines 4 and 5; *MenW-CRM Conjugate*, Page 22 of 43, Lines 3 and 4 from Bottom; *MenY-CRM Conjugate*, Page 22 of 43, Lines 3 and 4 from**

Bottom: Please confirm the numerical values for the volume of -----b(4)-----

7. 3.2.S.2.5 Process Validation and/or Evaluation, *MenA-CRM Conjugate*, Page 27 of 46, Line 15; *MenC-CRM Conjugate*, Page 29 of 48, Line 17; *MenW-CRM Conjugate*, Page 26 of 43, Line 15; *MenY-CRM Conjugate*, Page 26 of 43, Line 15:
-----b(4)-----

8. 3.2.S.2.5 Process Validation and/or Evaluation, *MenW-CRM Conjugate*, Page 19 of 43, Line 13; 3.2.S.2.2 Manufacturing Process and Controls, Page 9 of 18, First Column, Line 12; 3.2.S.2.2 Manufacturing Process and Controls, Page 14 of 18, Line 1; 2.3.S.2 Manufacture, Page 7 of 39, First Column, Line 12; 3.2.S.2.5 Process Validation and/or Evaluation, *MenY-CRM Conjugate*, Page 19 of 43, Lines 12-13; 3.2.S.2.2 Manufacturing Process and Controls, Page 9 of 18, First Column, Line 12; 3.2.S.2.2 Manufacturing Process and Controls, Page 14 of 18, Line 1; 2.3.S.2 Manufacture, Page 7 of 40, First Column, Line 12: ---b(4)---

9. 3.2.S.2.5 Process Validation and/or Evaluation, *MenW-CRM Conjugate*, Page 22 of 43, Line 11; *MenY-CRM Conjugate*, Page 22 of 43, Line 11: Please confirm the mass of “--b(4)-----
*CRM*₁₉₇

10. 2.3.S.1. General Information, Page 2 of 2, Line 8; 3.2.S.1.3 General Properties, Page 5 of 5, Line 6: Please confirm that CRM197 contains a --b(4)---

11. 2.3.S.2. Manufacture, Page 9 of 33: Line 16 Please confirm “-b(4)-----” instead of -b(4)---

12. 2.3.S.2. Manufacture, Page 14 of 33: Line 14 Please confirm the Measure unit “mg/ml” and the Acceptance criteria --b(4)-----

MenA-CRM Conjugate

13. 2.3.S.2 Manufacture, Page 10 of 38, First Column, Line 2: Please confirm the concentration of “-b(4)-” instead of “-b(4)---”

14. 3.2.S.2.5. Process Validation and/or Evaluation, Page 17 of 46: Table

3.2.S.2.5.1.1-4 Please provide a copy of SOP b(4) 07.189.

15. 3.2.S.2.5.Process Validation and/or Evaluation, Page 24 of 46, Lines 2: Please confirm that “-b(4)-” instead of “-b(4)-----” is used to --b(4)-----.

MenC-CRM Conjugate

16. 3.2.S.2.2 Manufacturing Process and Controls, Page 17 of 20, Line 4: Please confirm the concentration “-b(4)-” instead of “-b(4)---”.

17. 3.2.S.2.5 Process Validation and/or Evaluation, Page 29 of 48, Lines 15-16; 3.2.S.2.2 Manufacturing Process and Controls, Page 11 of 20, First Column, Lines 5-6; 3.2.S.2.2 Manufacturing Process and Controls, Page 17 of 20, Line 4; 3.2.S.2.3 Control of Materials, Page 8 of 11, First Column, Lines 11-14; 2.3.S.2 Manufacture, Page 9 of 39, First Column, Lines 5-6: Please clarify the condition of the --b(4)-----

18. **3.2.S.2.5 Process Validation and/or Evaluation, Page 30 of 48, Line 10:** Please clarify the use of “-----b(4)-----” instead of “-----b(4)-----”.

19. **3.2.S.2.5 Process Validation and/or Evaluation, Page 33 of 48, Line 11:** Please confirm “-----b(4)-----” instead of “-----b(4)----- was performed”.

MenW-CRM Conjugate

20. **3.2.S.2.5 Process Validation and/or Evaluation, Page 11 of 43:** Please provide a copy of SOP --b(4)-----.

MenA Lyophilized or MenA Lyo (lyophilized powder, vial, single dose)

21. **2.3.P.3 Manufacture, Page 5 of 8, Figure 2.3.P.3.2-1, Middle Column, Line 3; 3.2.P.3.3 Manufacture, Page 6 of 11, Middle Column, Line 3:** Please confirm the temperature -b(4)- instead of -b(4)-

RECOMMENDATION

Based on the complete review of the submitted CMC information and the Company's responses to the above comments in the submitted Amendments, I recommend that this BLA be approved.