

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH**

**DATE:** April 4, 2009

**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  
CRM<sub>197</sub> Conjugate Vaccine, Menveo<sup>®</sup>, Novartis

**TO:** File, STN 125300  
Cara Fiore, DVRPA, HFM-481  
Willie Vann, Committee Chair

**THROUGH:** Willie Vann, Ph.D., Chief, Laboratory of Bacterial  
Polysaccharides, DBPAP

**SUMMARY**

Novartis Vaccines and Diagnostics, Inc. is requesting for licensure of Meningococcal (Groups A, C, W-135 and Y) Oligosaccharide CRM<sub>197</sub> Conjugate Vaccine: Menveo<sup>®</sup>. Menveo<sup>®</sup> consists of one vial, containing the lyophilized MenA Conjugate Component, and one vial ---b(4)--- containing the liquid MenCWY Conjugate Component. The selected final formulation contains 10-5-5-5 ug per oligosaccharide of *N. meningitidis* serogroups A, C, W135 and Y, respectively, without adjuvant. The pharmaceutical form is powder and solvent for solution for injection. The dose is 0.5 mL (after reconstitution). Menveo<sup>®</sup> consists of four drug substances: Meningococcal group A oligosaccharide to *Corynebacterium diphtheriae* CRM<sub>197</sub> protein (MenA-CRM Conjugate), Meningococcal group C oligosaccharide to *Corynebacterium diphtheriae* CRM<sub>197</sub> protein (MenC-CRM Conjugate), Meningococcal group W-135 oligosaccharide to *Corynebacterium diphtheriae* CRM<sub>197</sub> protein (MenW-CRM Conjugate), Meningococcal group Y oligosaccharide to *Corynebacterium diphtheriae* CRM<sub>197</sub> 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<sub>197</sub>) and capsular polysaccharide (A, C, W-135 and Y obtained from *Neisseria meningitidis* serogroups A, C, W-135 and Y, respectively), for a total of 5 process intermediates, which are MenA, MenC, MenW and MenY polysaccharides and CRM<sub>197</sub>.

5 Pages determined to be not releasable:

b(4)

-----b(4)-----  
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**MenCWY Liquid (vial ---b(4)---)** – The composition of MenCWY Liquid (vial ---b(4)---) is MenC-CRM (5 ug MenC oligosaccharide, --b(4)-----), MenW (5 ug MenW oligosaccharide, --b(4)-----), MenY (5 ug MenY oligosaccharide, ----b(4)-----) -----

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

## **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<sup>®</sup> MenA Lyo needs to be included in their lot release specifications.
3. Please provide the SOP for --b(4)----- determination of each (MenA, C, W-135 and Y) conjugate and Menveo<sup>®</sup> 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)----- and the mass 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:** The -----b(4)----- of --b(4)----- is determined by -b(4)--- assay. It is noted that -b(4)-- method is used for -----b(4)----- in the --b(4)----- steps. The values of --b(4)----- of the conjugate will be affected by inconsistent methods -----b(4)----- . This confusion has to be clarified throughout the entire BLA submission. Please comment.
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:** Please confirm that the b(4) value “--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)” instead of “b(4)”.

***CRM<sub>197</sub>***

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)-----  
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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)-(alert limit).”

***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 perform --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)-----  
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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:** ---b(4)---  
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***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) 07.20, 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)