US Food & Drug Administration
Center for Biologics Evaluation & Research
Office of Compliance & Biologics Quality
Division of Manufacturing & Product Quality

MEMORANDUM – Final Review

To: Administrative File;
STN 125300/0 – Meningococcal ACWY Conjugate Vaccine, Menveo®

From: Joseph George
Consumer Safety Officer
CBER/OCBQ/DMPQ/MRB I, HFM-675

Through: Carolyn Renshaw
Branch Chief
CBER/OCBQ/DMPQ/MRB I, HFM-675

Cc: Willie Vann – Chair, CBER/OVRR/DBPAP/LBP, HFM-437
Nicole Trudel – Reviewer, CBER/OCBQ/DMPQ/ MRB I, HFM-675
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Elizabeth Valenti – RMP, CBER/OVRR/DVRPA, HFM-481

Applicant: Novartis Vaccines and Diagnostics, Inc. **US License Number:** 1751

Subject: Review of Novartis Vaccines and Diagnostics, Inc. BLA for Meningococcal ACWY Conjugate Vaccine, Menveo® indicated for immunization for 11-55 years of age for the prevention of disease caused by *N. meningitdis* serogroups A, C , W-135 Y.

ADD: 29 June 2009

I. Recommended Action:

Based on review of the original submission, relevant amendments, and our inspection, I recommend the two deficiencies detailed below (as previously requested of the firm in the 21 May 2009 Information Request) be included in a CR Letter.

II. Significant Review Issues:

1. *Prior to our arrival in Rosia, Italy for the Pre-Approval Inspection, Novartis informed us that their production schedule had changed in light of additional process validation work which needed to be performed due to a deviation with a MenW polysaccharide conformance lot. During the inspection it was found that a total of 4 MenW polysaccharide lots had failed to meet the specification for the ---------b(4)---------- As such, it was noted that manufacturing consistency had not been demonstrated. This issue was included on the 483 and was deferred to the product office for assessment and determining course of action and specific language for inclusion in a CR Letter.*

The following request was sent to Novartis on 21 May 2009. The firm has not yet provided a response and as such we are unable to perform a complete review of the Comparability Protocol for the addition of Building b(4) filling line -b(4)-. This request should be reiterated in a CR Letter to the firm.

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

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

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

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

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

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

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

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

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

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3. *In section 3.2.A.1.3.2.1 (--b(4)------ - MenA Lyophilized) reference is made to Cleaning Validation Report (CVR) 404926 for the --b(4)---------- vessels and CVR 224386 for the Filling set (pumps and needles). These validation reports were not included in the original submission or any subsequent amendment. In addition, the validation summaries provided in this section were not detailed enough to elicit a complete review. As such, please provide a more detailed summary of these two validation reports including but not limited to the number of studies performed, the acceptance criteria used for testing, the results, and a summary of any deviations encountered and corrective actions taken during the studies.*

4. *In section 3.2.A.1.2.1.2 (Rosia/-b(4)----) you have described your approach to equipment cleaning validation in general. Please provide the rationale for using the criterion of -b(4)---------- (for dedicated equipment) of the antigen present in the equipment during the manufacturing of the following lot for product and product/detergent carry-over. Please include details regarding how these levels of carry-over correlate to the specific analytical testing performed during the studies.*

III. Summary:

Novartis Vaccines and Diagnostics, Inc. (US License #1751) has submitted a BLA for their Meningococcal ACWY Conjugate Vaccine product, Menveo® indicated for immunization for 11-55 years of age for the prevention of disease caused by *N. meningitdis* serogroups A, C, W-135, and Y. Clinical investigations are on going to extend this indication to children below 11 years of age and are outside the scope of this BLA. This submission is in eCTD format and was received on 28 August 2008. Twelve amendments have also been submitted. They are as follows:

1. 21 November 2008 – information regarding the manufacture of the CRM protein as well as information pertaining to container closure extractables/leachables studies.
2. 05 December 2008 – clinical safety update on study V59P18.
3. 19 December 2008 – first response to 75-day deficiency letter.
4. 15 January 2009 – additional and complete responses to 75-day deficiency letter: included list of equipment and utilities' PQ list and attachments.
5. 06 February 2009 – responses to assay validation questions; final container protocol templates; revised facility floor plan and material flow; revised packaging mock-ups; final information on pregnancies in study V59P13; final immunogenicity data from study V59P17.
6. 24 February 2009 – supplementary report of the study V59P18.
7. 09 March 2009 – response to pharmacovigilance issues.
8. 30 March 2009 – correction of expressions of Action and Alert Limits (LIMS error); updated list of products formulated and/or filled in Building b(4) at the Rosia site.

9. 10 April 2009 – revised request for deferral of pediatric studies.
10. 17 April 2009 – FDA Form 483 responses.
11. 06 May 2009 – batch production records and documents provided with product samples submitted for pre-licensure testing.
12. 15 May 2009 – updated stability data; revised packaging mock-ups.
13. 17 June 2009 – revalidation of polysaccharide --b(4)------------
14. 22 June 2009 – protocol synopsis for post-licensure safety study; update to 483 responses; response to IR for filling line --b(4)-------

NOTE: A final draft of my complete review of this BLA was sent to management on 12 June 2009. As such review of amendments 13 and 14 is not included herein. This information will be reviewed during the next review cycle following issuance of the CR Letter before or on the 29 June 2009 Action Due Date.

Menveo® 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 µg per oligosaccharide of *N. meningitidis* serogroups A, C, W, and Y respectively, without adjuvant. The pharmaceutical form is powder and solvent for solution for injection. The dose is 0.5 ml (after reconstitution). Each of four drug substances 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, W135 and Y, respectively), for a total of 5 process intermediates, which are: MenA, MenC, MenW and MenY polysaccharides and CRM_{197}. Given the complexity of the manufacturing process and the controls carried out on the five process intermediates, each of them has been discussed in a separate 3.2.S section in module 3. Module 3 also contains two 3.2.P sections with information on MenCWY Liquid and MenA Lyophilized final product. Relevant information provide in these sections, as well as 3.2.A.1 Facilities and Equipment and 3.2.R Regional Information (Comparability Protocols), are the subject of my review.

IV. Drug Substance

The submission includes nine separate 2.3.S and 3.2.S sections corresponding to five process intermediates (CRM_{197}, MenA, MenC, MenW, and MenY polysaccharides) and four drug substances (MenA-CRM, MenC-CRM, MenW-CRM, MenY-CRM Conjugates). My review of each of these sections follows.

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

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

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

---b(4)---- ----------. In the manufacture of MenACWY vaccine, CRM_{197} is a process intermediate, which is then conjugated to MenA, MenC, MenW and MenY -b(4)---- oligosaccharides to give the drug substances: MenA-CRM, MenC-CRM, MenW-CRM, and MenY-CRM. CRM_{197} is presently used by the applicant in three vaccines licensed worldwide, but not in the United States (US):

- Vaxem Hib (*Haemophilus influenzae* type b (Hib) glycoconjugate vaccine) registered in Italy, United Kingdom (UK) and Hungary
- QUATTVAXEM (combined diphtheria, tetanus, pertussis and *Haemophilus influenzae* type b (Hib)) registered in Italy
- Menjugate® (Meningococcal Group C–CRM_{197} Conjugate Vaccine) registered in 20 European Union (EU) countries, Canada, Australia, and several other countries worldwide.

Process validation for CRM_{197} production was performed from May through June 2006 and is detailed throughout sections 2.3.S.2.5 and 3.2.S.2.5. The latter section included the following attachments related to process validation:

Process Step	Protocol	Report
---b(4)---------- **---b(4)----------** **---b(4)----------** **--b(4)----------** ---b(4)----------	CRM-197/026/40/PVP/06	CRM-197/026/40/PVR/06
---b(4)---------- **---b(4)----------** **---b(4)----------** **---b(4)----------** ---b(4)----------	CRM-197/026/40/PVP/03	CRM-197/026/40/PVR/03

As specified by the MenACWY Process Validation Master Plan (PVMP), individual process validation protocols (PVPs) were executed for each step of the process, and process validation reports (PVRs) were written and approved as listed above. A summary of results was tabulated in section 2.3.S.2.5. All validation reports were included in section 3.2.S.2.5.

A total of ----b(4)---------- were manufactured and tested in support of process validation. I reviewed the results of ---b(4)---------- testing in both sections. The acceptance criteria for these assays are tabulated below:

Process Step	Acceptance Criteria	Classification
---b(4)----------		
---b(4)----------	**---b(4)----------**	Critical
---b(4)----------	**---b(4)----------**	Non-critical
---b(4)----------		
---b(4)----------	**---b(4)----------**	Non-critical
---b(4)----------	---b(4)----------	Non-critical

6 Pages determined to be not releasable:

b(4)

V. <u>Drug Product</u>

A. MenA Lyophilized Conjugate Component (MenA Lyo) Manufacture (2.3.P.3 and 3.2.P.3)

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

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

- **Process Validation: --b(4)-Lyophilizer**

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

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

- **Process Validation: --b(4)--- Lyophilizer**

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

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

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

Container Closure (3.2.P.7)
The MenA Lyo component is presented in 2 mL vials. The following table summarizes the components of each final container.

Component	Material of Construction	Supplier and Reference DMF
Vial	---b(4)---------- ----------	---b(4)---------- ---------- ----------
Stopper	--b(4)---------- ----------	---b(4)----------
Flip-off	--b(4)----------	--b(4)----------

Container closure integrity testing (---b(4)----------) was performed. Validation studies were provided in Amendment 004 received on 15 January 2009. All validations were acceptable and were reviewed during inspection. Please see the EIR and N. Trudel's review memorandum for additional information.

Stability (3.2.P.8)
A total of b(4) lots in various developmental phases have been put on stability. The proposed shelf life is 36 months when stored at 2 – 8°C or at -b(4)-. Novartis has acquired up to 18 months at 2 – 8°C, ---b(4)---------- (accelerated) for three process validation lots --b(4)---------- (only 12 months of data has been provided) manufactured in June 2007. This data was provided in amendment 0012 received on 15 May 2009. Sterility and Container closure integrity was tested only at Time = 0 for lots stored at 2 – 8°C and -b(4)-. Only container closure integrity was tested at --b(4)---------- ---------- time points for samples held at both --b(4)----------. All results passed and no deviations were reported. I defer all other testing results to the product office for review.

Novartis has committed to completing their stability protocol through -b(4)----- at 2 – 8°C or at b(4) Sterility and Container Closure Integrity testing will be included in the 24, 36, and b(4) -----

------- stability testing panel. In addition they will put one commercial lot per year into their routine stability protocol.

B. MenCWY Liquid Conjugate Component (MenCWY Liquid) (2.3.P.3 and 3.2.P.3)

Manufacture

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

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

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

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

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

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

Process Step	Protocol	Report

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

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

Container Closure (3.2.P.7)
The MenCWY conjugate component is presented in single-dose --b(4)---------- ---------- -------- 3 mL glass vials. The following table summarizes the components of each final container.

Component	Material of Construction	Supplier and Reference DMF
Vial	--b(4)--- ----------	--b(4)----------
Stopper	-b(4)- ----------	--b(4)----------
Flip-off	--b(4)----------	--b(4)----------
-b(4)-----	--b(4)-- ----------	--b(4)----------
---b(4)----------	--b(4)--- ----------	--b(4)----------
-b(4)--	--b(4)--- ----------	--b(4)----------
--b(4)----	--b(4)----------	--b(4)----------

Container closure integrity testing (---b(4)----------) was performed on--b(4)-- vial -b(4)----- configurations. These validation studies were provided in Amendment 004 received on 15 January 2009. All validations were acceptable and were reviewed during inspection. Please see the EIR and N. Trudel's review memorandum for additional information.

Stability (3.2.P.8)
A total of b(4) lots at various developmental stages -----b(4)---------- (vial --b(4)----) have been put on stability. -b(4)- lots representing the current manufacturing process and used for process validations of --b(4)---------- vials, were included in this stability study to establish the product dating period. Sterility and Container Closure Integrity is tested at time --b(4)----------. Novartis proposes a 36 month shelf life when stored at 2 – 8°C or -b(4)----.
Also, ---------b(4)----------.
All stability results were passing.

VI. Facilities and Equipment

Drug substance and drug product manufacturing occurs in Rosia, Italy. This includes formulation, filling and inspection of MenC-CRM, MenW-CRM and MenY-CRM (MenCWY Liquid). Formulation, filling, and lyophilization of MenA lyophilized conjugate component (MenA Lyo) is carried out at the Novartis --b(4)---------- site. However, inspection, labeling and packaging of MenA Lyo is carried out at the Rosia site in Building b(4). The -b(4)- site is utilized only for a portion of the Menveo QC testing.

[b(4)]

All the proposed facilities are classified as multi-use. However, some of the buildings include areas that are dedicated to the production of a given intermediate and/or product. The details for the shared/dedicated uses for each building are described in the specific building/processing sections. Review of each of these sections follows.

A. Rosia & -b(4)-, Italy Facilities

Novartis Vaccines and Diagnostics S.r.l (Novartis Vaccines) performs manufacturing of vaccines at the Rosia and -b(4)-, Italy sites. Products at the Rosia Site are manufactured in dedicated areas on a campaign basis. The Rosia site currently employs approximately b(4) personnel for Menveo production and QC testing. The Rosia and -b(4)- facilities being proposed for licensure are listed in the table below.

Building or External Facility	Manufacturing Operation
ROSIA or -b(4)-	
Building b(4) (Rosia)	--b(4)----------
Building b(4) (Rosia)	--b(4)---------- ---------- Manufacturing

Building b(4) (Rosia)	MenCWY Formulation/ Filling /Inspection (vial)
Building b(4) (Rosia)	MenA (vial) and MenCWY (-b(4)--- Inspection, Labeling and Packaging
Buildings b(4)(Rosia), b(4) (Rosia), b(4) (Rosia)	Warehouse/Storage/Raw Materials
Buildingb(4)(Rosia), b(4) (Rosia), b(4) and b(4)	Quality Control

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

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

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

Novartis provided a list of all major/critical equipment and their respective validation status. Building b(4) utilities have been reviewed and are described later in this memorandum.

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

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

- **CRM_{197} Manufacturing**

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

- **Polysaccharide Manufacturing (MenA, C, W, Y)**

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

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

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

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

- **Oligosaccharide-CRM Bulk Manufacturing**

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

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

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

- **Equipment**

Major/Critical equipment was listed with their corresponding validation status in section 3.2.A.1.2.2.2.6. This equipment includes -b(4)--------- tanks, columns, centrifuges, autoclave, parts and glassware washer, --b(4)----------. Validation of these pieces of equipment were verified and reviewed during our inspection. No objections were noted. Please see EIR for addition details.

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

Cleaning Validation (CV) was performed on equipment used for the manufacturing of the drug substances and related process intermediates. For non-dedicated equipment, a matrix approach was used and the same cleaning validation methodology was used for equivalent or similar equipment used at a particular step (i.e. -b(4)- for each antigen, for a total of b(4) runs). Novartis states that this approach is supported by the fact that these drug substances have similar physiochemical characteristics (especially solubility), making the matrix approach feasible.

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

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

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

The following request was sent to the firm on 24 June 2009:

- *In section 3.2.A.1.2.1.2 (Rosia/-b(4)-) you have described your approach to equipment cleaning validation in general. Please provide the rationale for using the criterion of -b(4)---------- (for dedicated equipment) of the antigen present in the equipment during the manufacturing of the following lot for product and product/detergent carry-over. Please include details regarding how these levels of carry-over correlate to the specific analytical testing performed during the studies.*

Detailed descriptions of utilities and their respective validations are included later in this review.

3. Formulation, Filling and Visual Inspection (vials) – Building b(4) (2.3.A.1.2.2.1,

Manufacturing activities in Building b(4) include formulation, vial -------b(4)-- filling, and visual inspection of vials for MenCWY Liquid. Building b(4) is a multi-product facility. Building b(4) utilities are supported from Buildings -b(4)-, which include systems for --b(4)----------.

Manufacturing activities are summarized below.

- **Formulation of MenCWY Liquid**

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

- **MenCWY Liquid Vial Filling and Inspection**

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

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

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

- **Media Fills**

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

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

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

Vial Line, -b(4)-----
A Media Fill validation study for fill line -b(4)-- was performed and summarized in Validation Report Media Fill/42/057/-b(4)----/PVR/00 approved on 6 November 2006. This report was provided in the BLA amendment 004 received on 15 January 2009. The study was conducted from 28 July to 14 September 2006. Three media fills using b(4) of at least -b(4)- vials were performed under the same conditions described above. The third run found one contaminated vial thus an additional, 4th run, was performed successfully. The deviation associated with the contaminated vial was reviewed during inspection. I had no additional comment.

- **Equipment**

The following equipment is found in Building b(4) associated with Menveo manufacturing:

- Vial washer
- --b(4)----------
- Autoclave
- Vial Filling line -b(4)-------
- ---------- -b(4)----

- Bulk vessel – --b(4)----------
- --b(4)----------

Equipment has been validated. Shared equipment validations were not reviewed herein as they were covered in a previous submission (STN 103837/5316). Dedicated equipment used for Menveo® manufacturing was review during our inspection and no issues were found. Please see the EIR for additional details.

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

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

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4. Visual Inspection, Packaging/Labeling – Building b(4) (2.3.A.1.2.2.2 and 3.2.A.1.2.3.2)

There are three Menveo operations performed in Building b(4):

1. ---b(4)----------
2. --b(4)- ----------
   ---
3. --b(4)----------

All operations are conducted in controlled unclassified environments. This is a multi-product building and Novartis states that line clearance procedures are in place to ensure product mix ups do not occur.

Inspection Machine --b(4)---------- are used for MenCWY Liquid -b(4)--- and MenA Lyo vials respectively. Packaging Line b(4) will be used for vial/vial presentation ----------
---------- -b(4)----------

Visual inspection validation was covered in detail during our inspection and no issues were found. Please see the EIR.

5. HVAC (3.2.A.1.2.4.3-1 through 5)

Novartis included a description Building ---b(4)---------- HVAC system and validation in section 3.2.A.1.2.4.3 Attachments 1 through 5 respectively.

Each building's HVAC system validation included IQ, OQ, and PQ. OQ included -b(4)--------b(4)----------. Results were summarized however ----b(4)---------- data was not included. PQ was carried out over a 3-week period. PQ included --b(4)----------. Acceptance criteria were presented which I found appropriate according to ISO 14-644-1 and EU guides. The firm stated that the results of viable and non-viable monitoring and physical parameters --b(4)----------) were analyzed and discussed in the relevant PQ reports; any deviations that occurred were investigated and corrective actions (if necessary) were taken.

Novartis states that HEPA filters in the Grade b(4) and Grade b(4) areas are tested every b(4) months for integrity. After a facility shutdown, ----b(4)---------- are monitored by the --b(4)----------. The HVAC systems are not released for production unless all results are satisfactory.

6. Water Systems (3.2.A.1.2.4.3-6 through 8)

Water systems including Purified Water (PW), Water for Injection (WFI) and Clean Steam (CS) for building -b(4)------- are described including a summary of validations performed in section 3.2.A.1.2.4.3 Attachments 6 through 8 respectively.

- **Building b(4)**

Purified Water --b(4)----- is produced and supplied by --b(4)---------- systems have been validated and a summary of IQ, OQ, and PQ were provided. Each Performance Qualification was conducted over the course of 4 weeks. Minimum and Maximum results were tabulated in this section in Attachment 6, Tables 4.3-5 and 4.3-10. All testing met acceptance criteria and no deviations were noted. Routine testing will use the following specifications:

[b(4)]

- **Building b(4)**

Building b(4) water systems include purified water (PW), water for injection (WFI), and clean steam (CS). Each system was fully described including all sampling and points of use. Validations studies for each of the three systems included IQ, OQ and PQ which was performed in 3 phases. Each phase consisted of progressively less frequent monitoring while increasing the length of the observation period. This is described in the table below.

[b(4)]

Summary data was provided in Attachment 7, Tables 4, 8, and 13 for PW, WFI, and CS respectively. Data included acceptance criteria; total number of samples per test; % conformity; maximum value; and mean value. Purified Water results all met acceptance criteria (-b(4)----------) which were of appropriate limits according to USP and EP. WFI and CS PQ results were higher than 99% conformity. Novartis states that all deviations during the study were investigated and corrected. I found the results acceptable and limits appropriate according to USP and EP.

- **Building b(4)**

Building b(4) water systems include PW, WFI and CS. Each system was fully described including all sampling and points of use. Validations studies for each of the three systems included IQ, OQ and PQ which was performed in 3 phases. Each phase consisted of progressively less frequent monitoring while increasing the length of the observation period in the same manner used for Building b(4) valdiations.

Summary data was provided in Attachment 8, Tables 4.2-3 through 4.2-14 for PW and WFI and 4.3-3 through 4.3-14. Data included acceptance criteria; total number of samples per test; and minimum and maximum values. I found the results acceptable and Novartis states that all deviations were fully investigated and resolved.

Routine testing follows the schedule below.

[b(4)]

[b(4)]

Trending data was obtained and reviewed during our inspection. Please refer to the EIR for details.

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

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7. Environmental Monitoring

The established environmental monitoring program for all critical areas complies with FDA, EU and ISO 14644-1 standards, and is summarized in SOP 201430 "*General Procedure for Environmental Control*." This procedure includes the following action limits for EM samples:

[b(4)]

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

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

[b(4)]

1. MenA Lyo Vial Formulation/Filling/Lyophilization – Building b(4) (2.3.A.1.3.1 and 3.2.A.1.3.2.1)

Building b(4) is a multi-product facility previously licensed by the FDA and other regulatory agencies for the manufacture of approved vaccines and other biological products, including sera and test allergens. The facility has been inspected by the FDA (most recently in October 2008 by Team Biologics) and by other regulatory agencies in connection with other licensed products manufactured in -b(4)-----. Non-pharmaceutical products are not manufactured or processed at the --b(4)---- site. Novartis states that the following contamination and cross contamination controls are in place:

- After each formulation/filling, a complete cleaning and disinfection procedure (changeover) is carried out.
- Each formulation suite has its own HVAC units and material and personal locks.
- No viable organisms, such as virus or bacteria, are handled in the Formulation and Filling suites and antigens are handled in closed containers.
- The mobile equipment used for MenA-CRM in the Formulation and Filling areas is dedicated.
- All equipment is labeled in accordance with current standards of GMP and Novartis written procedures.
- All bulk containers are labeled in accordance with current standards of GMP and Novartis written procedures.
- Cleaning validation has been performed to verify that the procedures are adequate for cleaning the applicable equipment.
- Freeze dryer b(4) is equipped with a --b(4)--------- which is qualified. -b(4)- freeze dryers are validated for cleaning.
- Only single-use tubing and materials like filters are used during production.
- There is a unidirectional flow of personnel and materials through the air locks to the sterile core area.
- The air pressure cascade between the clean rooms creates a unidirectional air flow.
- Written gowning and hygiene procedures are in place.

- Operators are specifically trained before working in the area and they are monitored when working in the area.

- **Formulation of MenA-CRM**

Formulation of MenA-CRM is performed in the Formulation b(4)or Formulationb(4) area.The other marketed products (both US-licensed and non-US-licensed) processed in Formulation b(4) are Rabies Vaccine, MenC-CRM Conjugate Vaccine, Influenza Split and Subunit Vaccines and Tick Borne Encephalitis Vaccine. The following developmental products are also processed in Formulation b(4) area: ---b(4)----------. In Formulation b(4) the following marketed products are also processed: Diphtheria, Tetanus and Pertussis containing combination vaccines, Diphtheria and Tetanus containing bulk concentrates for further manufacturing use, MenC-CRM Conjugate Vaccine and Botulism antitoxin, an emergency drug against Botulism toxification. Both formulation areas have Class b(4) surrounded by Class b(4) environments.

A list of major/critical equipment was provided in Table 3.2.A.1.3.2.1.5-1. This table included validation status of shared equipment such as autoclaves, --b(4)----------, and laminar flow units. The table also included the b(4) formulation/final bulk container which is dedicated for Menveo. Cleaning validation of this container was described in detail.

The --b(4)-- ---------- Cleaning validation was performed with three consecutive runs under worst-case conditions using Menjugate (MenC-CRM Conjugate Vaccine, a non-US licensed product) which is similar in content and concentration to MenA-CRM. Acceptance criteria and the results of this cleaning validation study was not summarized in the original submission. Only reference to the Cleaning Validation Report, CVR 404926 and Amendment 404926 were given. Novartis only states that the validation was successful. The following was requested of the firm on 24 June 2009:

- *In section 3.2.A.1.3.2.1 (-b(4)------ MenA Lyophilized) reference is made to Cleaning Validation Report (CVR) 404926 for the --b(4)---------- and CVR 224386 for the Filling set (pumps and needles). These validation reports were not included in the original submission or any subsequent amendment. In addition, the validation summaries provided in this section were not detailed enough to elicit a complete review. As such, please provide a more detailed summary of these two validation reports including but not limited to the number of studies performed, the acceptance criteria used for testing, the results, and a summary of any deviations encountered and corrective actions taken during the studies.*

- **Vial Filling and Lyophilization for MenA-CRM**

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

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

A list of major/critical equipment with validation status was provided in Table 3.2.A.1.3.2.1.5-4. The table included filling equipment such as the crimping machine, filling machine, autoclave, -b(4)----------, vial washer, lyophilizers, and equipment washers. These items are shared. The only dedicated equipment used in filling is the filling needles and pumps. Novartis states that cleaning validation has been performed and was reported in CVR 224386. Acceptance criteria and summary results were not provided in the original submission. Novartis only states that the validation was successful. Further details were requested of the firm on 24 June 2009. The specific request is in the section above.

VII. Shipping Validations

MenA-CRM shipment to Marburg has been validated. This was reviewed during inspection. Please see the EIR for details. Final product shipped to the US is ongoing. This was reviewed during inspection and a 483 observation was noted. The firm has provided an acceptable response to the observation indicating that they will be providing complete validation data once available which they estimated completion by 31 May 2009. The information was actually received in Amendment 14 on 22 June 2009 and was not reviewed at the time of this memo. The information will be reviewed during the next review cycle.

VIII. Comparability Protocols

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

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

1. --b(4)----------
2. --b(4)----------
3. --b(4)------- ----------

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

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

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

- --b(4)-- ----------.
- --b(4)----- ----------
- --b(4)0----------
- --b(4)---- ----------.
- --b(4)-- ----------
- --b(4)------ ----------
- --b(4)-- ----------.

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

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

2. **Process validation including comparison of results to clinical study and b(4) batches and identification of any impact on release specifications**

Process validations for both formulation and fill processes will be performed in order to verify that the operations using b(4) will produce MenCWY Liquid drug product that meets specifications and is comparable to clinical trial and b(4) batches.

- **Formulation**

Process validation for Formulation is described in the protocol b(4) Form_--b(4)----------023/42/PVP/01 attached to this submission. b(4) has a maximum batch size of -b(4)---- of formulated bulk; therefore, a validation of the bulk formulation at this scale is necessary (note that the minimum batch size, b(4) has not changed and, therefore, does not require additional validation). Since the BPR is written to allow a variable batch size and the mixing and formulation tanks currently used will accommodate a -b(4)- batch, no equipment or process changes will be required to implement the scale-up according to the firm.

A total of three full-scale (-b(4)-) batches will be formulated according to the procedure mentioned above. --b(4)---------- will be used to challenge the process. In

addition to normal sampling for routine in-process and release testing, sampling will be performed for --b(4)---------- in order to assess sample homogeneity. The acceptance criteria follow:

Parameter	Acceptance Criteria	Classification
--b(4)---- ---------- ----------	-b(4)-----	Critical
-b(4)---- ---------- ----------	-b(4)-----	Critical
--b(4)-- ---------- ----------	-b(4)-----	Critical
--b(4)----------	-b(4)-----	Critical
--b(4)-- ---------- ----------	-b(4)-----	Critical
--b(4)--- ---------- ----------	-b(4)-----	Critical
--b(4)-- ---------- ----------	-b(4)-----	Critical
--b(4)--- ---------- ----------	-b(4)-----	Critical
--b(4)-- ---------- ----------	-b(4)-----	Critical
--b(4)--- ---------- ----------	-b(4)-----	Critical

The criteria above are identical to those used for the validation of -b(4)-----.

- **Filling**

The Filling process validation is described in the protocol b(4)_Filling_b(4)----------/023/42/PVP/00 attached to this submission. A total of three batches of --b(4)---------- (-b(4)- of final formulated bulk) will be run in support of this process validation.

In addition to normal sampling for routine release testing, increased sampling will be performed for --b(4)----------) in order to assess sample homogeneity. Increased samplings will occur at the --b(4)---------- ---------- of all three runs. The acceptance criteria that will be used are listed in the table below.

Parameter	Acceptance Criteria	Classification
--b(4)----------	-b(4)-----	Critical
--b(4)----------	-b(4)-----	Critical
--b(4)----------	-b(4)-----	Critical
--b(4)----------	-b(4)-----	Critical

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

The criteria above are identical to those used for the validation of --b(4)-----

In addition, the results will be compared to the release and process validation results obtained for the clinical and -b(4)---------- batches to ensure that the processes and resultant materials using b(4) are comparable. Acceptance criteria (e.g. statistical) for this comparison were not included.

- *You state that filling process validation results for b(4) will be compared to process validation results obtained for clinical and -b(4)---------- batches. Please provide the acceptance criteria for this comparison. How will this comparison be documented?*

Additional information also requested includes:

- *Please clarify where visual inspection will be performed for Meningococcal ACWY Conjugate Vaccine final container --b(4)---------- filled on --b(4)-----*

- *Please describe how you will evaluate stability of Meningococcal ACWY Conjugate Vaccine filled on -b(4)-. Your stability testing panel should include container closure integrity testing.* ***[product office input needed]***