DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

To: Administrative File: STN 125300, DCC Login ID 448295, Meningococcal ACWY Conjugate Vaccine (Menveo®)

Willie Vann, Chair, OVRR/DBPAP

Cara Fiore, RPM, OVRR/DVRPA

Joseph George, Inspection Lead, OCBQ/DMPQ/MRB I

CC: STN 125300 Review Committee

From: Nicole Trudel, CMC Facility Reviewer, OCBQ/DMPQ/MRB1

Through: Carolyn Renshaw, Branch Chief, OCBQ/DMPQ/MRB1

Subject: Review Memo: BLA, New vaccine for the prevention of disease caused by *Neisseria meningitidis* serogroups A, C, W-135, and Y

Indication: General product indication: Immunization for 11-55 years of age

Applicant: Novartis Vaccines and Diagnostics, Inc. Facility Sites: Rosia and -b(4)--, Italy, and --b(4)------

Due Date: June 29, 2009

Items Reviewed

- BLA 125300
  - 2.3.A.1 Facilities and Equipment
  - 3.2.A.1 Facilities and Equipment
- Amendment 125300/0.1: Summary of leachable studies (vial and syringe)
- Amendment 125300/0.3: Response to 75-Day Deficiencies Letter
- Amendment 125300/0.4: Additional Response to 75-Day Deficiencies Letter
  - 1.11.4 Second Response to FDA Deficiency Letter
  - 3.2.A.1 Rosia
  - 3.2.A.1 --b(4)-----

- Amendment 125300/0.5: Container protocol templates, revised floor plan and material flows
- Amendment 125300/0.8: BLA correction of alert/action limits
- Amendment 125300/0.10: Response to FDA 483
- November 26, 2008 Teleconference w/ the firm

Product Description

Menveo® (also referred to as MenACWY) is a Meningococcal (Groups A, C, W-135 and Y) Oligosaccharide CRM_{197} Conjugate Vaccine for immunization of individuals ages 11-55 years for the prevention of invasive meningococcal disease caused by *N. Meningitidis* serogroups A, C, W-135, and Y. Menveo® is currently undergoing additional clinical studies to support immunization for children under 11 years of age, but this indication is not within the scope of the subject BLA.

Drug Product: Final product contains two components:

- One vial with lyophilized MenA Conjugate Component (MenA Lyo)
- One vial --b(4)--- containing liquid MenCWY Conjugate component (MenCWY Liquid)

Final formulation contains 10, 5, 5, and 5 µg per oligosaccharide of *N. meningitidis* serogroups A, C, W, and Y, respectively, without adjuvant. Dose after reconstitution is 0.5 ml. There are four drug substances.

Drug Substance: Each of the four drug substances are comprised of one of the four capsular polysaccharides (A, C, W-135, and Y) conjugated to *Corynebacterium diphtheriae* Cross Reactive Material 197 (CRM_{197} protein):

- MenA-CRM Conjugate
- MenC-CRM Conjugate
- MenW-CRM Conjugate
- MenY-CRM Conjugate.

Process Intermediates:

- MenA polysaccharide
- MenC polysaccharide
- MenW polysaccharide
- MenY polysaccharide
- CRM_{197} Protein

Environmental Analysis:

Novartis applied for a waiver of an environmental analysis based on the categorical exclusion as described under 21 CFR 25.31(c), which applies to products containing substances that occur naturally in the environment, provided the introduction of these products does not significantly alter the concentration or distribution of the substances, their metabolites, or degradation products in the environment. Novartis states that the product itself is metabolized, and that when excreted, is indistinguishable from the body's other by-products. They also state that the inorganic salts eventually become untraceable in the environment. Based on this justification provided in Section 1.12.14 of the BLA, I find this waiver acceptable. This assessment is also documented in the Environmental Analysis Assessment review memorandum by Joseph George.

Summary

I recommend that a Complete Response letter be issued and that approval be deferred until such time that all CR issues are resolved. Numerous process validation issues, stability, labeling, and other product issues were discovered during the review and inspection process for this file. There are also open issues associated with the comparability protocols submitted under the regional (2.3.R.2) section of this eCTD. A draft CR letter is currently under review and is expected to be submitted to Novartis before the end of the current review cycle (June 29, 2009).

Novartis submitted the subject BLA electronically for a new meningococcal vaccine on August 28, 2008 (Received by the agency August 29). The scope of my review is limited to facilities and equipment and related CMC issues. I have deferred the review of the comparability protocols to J. George. Please refer to his review memorandum for details.

Process Flow Summary

The following is a summary of the Menveo® process flow. Please note that the steps are numbered for ease of reading, and do not necessarily correlate to the steps numbered in the submission.

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

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

Incoming Materials

All incoming materials are received, sampled, and stored in Building --b(4)---------- at the Novartis Rosia site. Materials are controlled through b(4), an automated inventory bar-code system. The status and expiration of every material item is tracked in b(4). All materials are bar-coded, and can be scanned with a bar-code reader for real-time status information.

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

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The warehouse contains designated areas for receipt, inspection, quarantine, release, QC sampling, weighing, dispensing, and shipping. Incoming materials are quarantined (and coded as such), pending release based on applicable sampling and test results. Rejected materials are also quarantined until they are disposed of or released. All approved materials are appropriately stored and are used on a first in/first out basis. Lots of incoming materials are tracked and updated with each use for reconciliation purposes.

Some of the more critical raw material items, the --b(4)----------, are tested in accordance with the Novartis Quality Manual, *Determination of the Bioload in Primary Packaging Materials for Drug Products*. The initial qualification of these --b(4)--- consists of testing multiple lots per this procedure. After the initial qualification, a requalification is performed periodically. Please refer to the EIR for additional detail on the qualification of this component.

Other critical components, the --b(4)----------material, were also reviewed on inspection. The supplier, --b(4)----, has been qualified and the bottles are accepted based on their Certificate of Analysis (C of A).

Issue: The qualification of these bottles has not been complete, as noted in Observation #8 of the FDA 483. A change request has been opened to introduce testing on three lots of an unrelated product and then --b(4)---- thereafter, but does not address Menveo® and has yet to be complete. It also does not address other storage vessels used for critical hold steps in the Menveo® manufacturing process. Furthermore, the C of As reviewed on inspection did not include verification of sterility or pyrogen testing acceptability. Extractables and leachables studies have also not been performed.

Resolution: Novartis responded to this issue in Amendment 10 to this BLA. They have now completed analytical method validation and have set specifications for -----b(4)---------- testing. They have also established SOP MA 03.041, *Analysis of Containers, Sterile and Other Material*, effective March 27, 2009. Three new lots will be fully tested and released with the anticipated completion date of June 15, 2009.

It should also be noted that the firm was cited during their February 4-11, 2008 inspection, Observation #2, for inadequate confirmation of their vendor's analysis.

Adequacy of materials management at the Rosia site was verified during the inspection. All materials (except for those noted above) were appropriately received, sampled, segregated, and stored in accordance with written procedures to ensure proper control and to prevent mix-ups. Please see the EIR for additional warehouse details.

Cell Banks (3.2.A.1.2.2.1)

Master and Working Seed Banks (MSB/WSB) ----b(4)--- ----------

Issue: During the inspection we discovered that the master and working seed bank metal containers were not clearly labeled or readable. The contents of the ---b(4)---------- for multiple products) and the specific locations of each seed bank within the --b(4)--- could not be easily determined. This storage and identification information was fragmented across several log books. Orderly storage of seed cultures and clear identification of seed cultures are required per CFR 610.18(a) and 610.18(b), respectively. This observation was documented as item #10 on the FDA 483 issued on February 27, 2009.

Resolution: The firm adequately responded to this observation in amendment 125300/0.10, received by the agency on April 17, 2009. They identified new labels that would remain intact at very low temperatures, and after a period of testing, they implemented the use of these labels on March 3, 2009. They have also revised SOP #201584 for the management of inventory of master and working seed banks, also effective March 3, 2009. Based on this revised procedure, Novartis states that the location and identification of their seed banks are much more readily accessible and orderly-----b(5)----------.

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

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

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

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

limits. The cleaning procedures for b(4) are the same as those followed for all production areas at the Rosia site. As noted above, facility cleaning was reviewed during the inspection. Please refer to the general facility cleaning section of this memorandum and the EIR for additional detail.

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

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

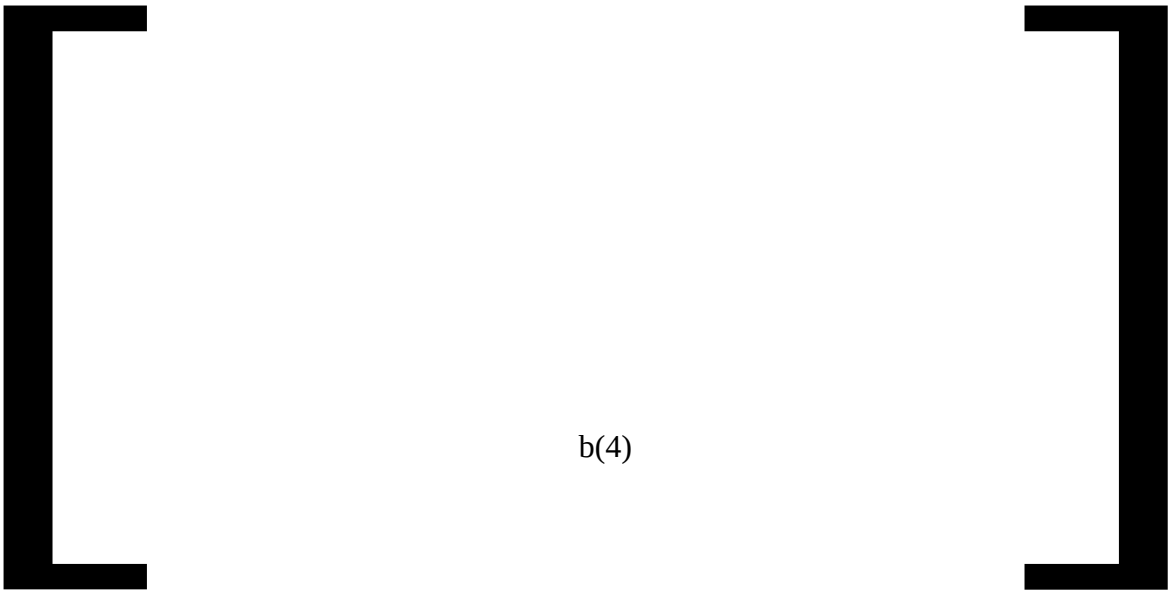
---b(4)---- ----------

Drug Substance Production - Building b(4)(2.3.A.1.2.1.2)

Building -b(4)---- is a multi-product facility. Established controls for the prevention of mix-ups and cross-contamination include limited access to authorized personnel only, environmental monitoring and control, validated cleaning procedures, use of closed systems where possible, easily cleaned and sanitized materials of construction, and segregation of product and intermediates. The CRM_{197} production areas of this building are dedicated. The polysaccharide production areas are shared with a ---b(4)---------- on a campaign basis; they also share freezer storage space.

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

-b(4)-CRM_{197} batches were produced to support the process validation. I will defer the majority of the process validation review to the product office, but the following is a summary of the critical control steps that I included in my CMC review, with their corresponding acceptance criteria and process validation results:



All acceptance criteria were met, with the exception of the --b(4)---------, which was investigated and resolved.

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

-b(4)-Polysaccharide batches were produced for each of the four serotypes to support the process validation. I will defer the majority of the process validation review to the product office, but the following is a summary of the critical control steps that I included in my CMC review, with their corresponding acceptance criteria and process validation results:

[b(4)]

As indicated by the data in the table above, all acceptance criteria were met for all lots, except for Batch --b(4)----------

Issue: Process validation is in adequate in that one of -b(4)---- PV lots for MenW failed to meet the -b(4)---- acceptance criterion of --b(4)-----. This indicates that the formaldehyde addition --b(4)---- is ineffective for MenW. This issue was documented in Observation 1 of the FDA 483 issued on February 27, 2009.

Resolution: This issue is documented as deficiency #1a in the draft Complete Response letter, scheduled to be sent to Novartis prior to the action due date for this file; the review clock will be stopped until Novartis adequately corrects and responds to this issue. As acknowledged on the 483 and

subsequent responses (from the firm) to the 483, corrective actions are ongoing. They include revalidation of the specific -b(4)---------- assay performed after the addition of the formaldehyde, revalidation of the --b(4)------ assay performed after the --b(4)---------- step, repeat process validation runs for MenW, and revalidation of the aforementioned specific assays as used in the production of MenA, MenC, and MenW.

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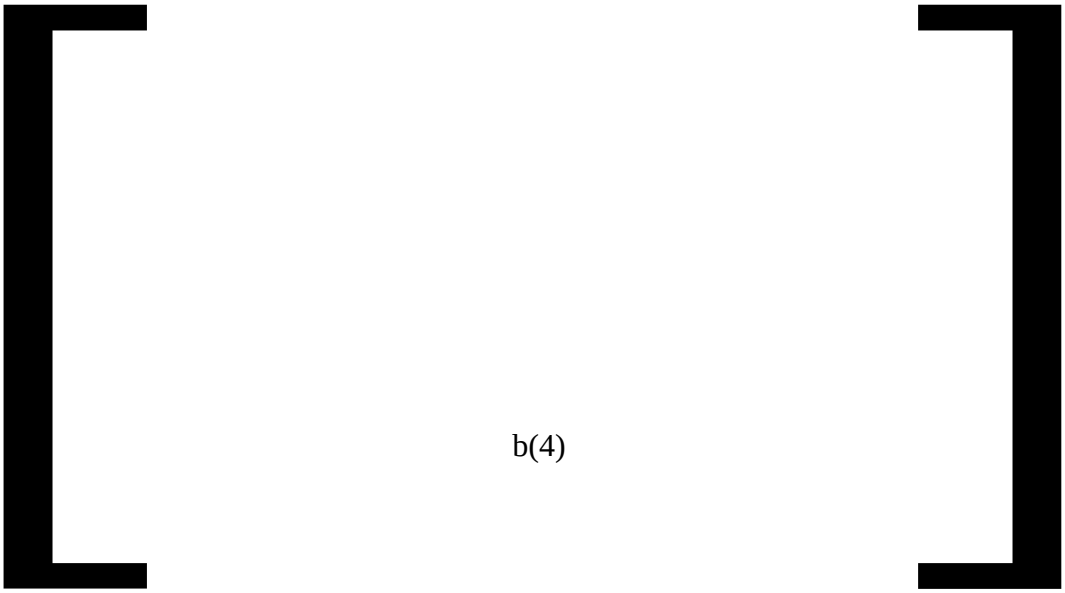
--b(4)---- ----------

Three conjugated bulk batches were produced for each of the four serotypes (MenA-CRM, MenC-CRM, MenW-CRM, MenY-CRM) to support the process validation. All pre-determined acceptance criteria were met. I will defer the majority of the process validation review to the product office, but the following is a summary of the critical control steps that I included in my CMC review of the -b(4)---- bulk conjugates, with their corresponding acceptance criteria and process validation results:

[b(4)]



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

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Facility cleaning in b(4) is performed in accordance with SOP #226737-05, *Sanitization of controlled and classified areas, b(4),* effective February 12, 2009, approved February 11, 2009. The following cleaning agents were appropriately qualified and are approved for use in b(4):

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Facility cleaning was reviewed during the inspection. Please refer to the EIR for additional details.

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

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

Drug Product Production - --b(4)-----

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

MenA Lyophilized drug product final container is a 2 mL glass vial with a --b(4)------- stopper and --b(4)---------- flip-off cap. See the Final Drug Product Container Closure write-up in the Drug Product Production -b(4)---- section of this memorandum for integrity testing of the MenA Lyophilized vials.

MenA-CRM Final Formulation Process Validation

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

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included in my CMC review of the MenA-CRM final formulation, with their corresponding acceptance criteria and process validation results:

[b(4)]

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

Drug Product Production – Building b(4)

B-b(4)is a multi-product facility with appropriate design and procedure controls in place to prevent mix-ups and cross-contamination. Controls include limited access to authorized personnel, a centralized automated environmental monitoring system, HVAC controlled environments, and appropriate product, personnel, materials, and waste flows to ensure proper segregation. ----b(4)-- ----------

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

MenCWY Liquid is filled into either a 3 mL glass vial ---b(4)----------and the vials are washed and sterilized in-house. The vial washer was qualified per *PQ Report for the Vial Washer --b(4)----* ----------. Worst-case conditions were incorporated into each of the three qualification runs to include ---b(4)--- ----------

The 3 mL glass vials in which MenCWY Liquid can be filled are ---b(4)------ ----------
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Formulation Process Validation

Three MenCWY Liquid drug product batches were produced to support the formulation process validation. All pre-determined acceptance criteria were met. I will defer the majority of the process validation review to the product office, but the following is a summary of the critical parameters that I included in my CMC review of the MenCWY Liquid drug product formulation, with their corresponding acceptance criteria and process validation results:

[b(4)]

Fill/Finish Process Validation

Three MenCWY Liquid drug product batches were produced to support the fill/finish process validation for the vial --b(4)---------- minimum and maximum lot sizes; b(4) minimum and b(4) maximum batch sizes were generated for each presentation. All pre-determined acceptance criteria were met. I will defer the majority of the process validation review to the product office, but the following is a summary of the critical parameters that I included in my CMC review of the MenCWY Liquid drug product fill/finish, with their corresponding acceptance criteria and process validation results:

[b(4)]

Final Drug Product Container Closure

MenCWY Liquid drug product final container can be either a 3 mL glass vial with a -b(4)- stopper and --b(4)---------- flip-off cap, ----b(4)----------
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Container closure integrity testing (CCIT) and extractables/leachables testing for both drug product components (MenCWY Liquid and MenA Lyophilized) were reviewed during the inspection. The following is a summary of that review, but please see the applicable EIR for more detail.

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

The firm performed extractables/leachables studies with appropriate solvents to represent worst-case conditions. The final container closure combinations were found to have no impact on the product during leachables studies.

Issue: The compound --b(4)---------- was detected in the amount of --b(4)---------- in the solvent used in the stopper/vial extractables study. The firm performed and/or may still be performing a toxicological assessment on these findings.

Resolution: This issue has been deferred to the toxicological review team for this BLA and will be addressed as a review issue throughout the ongoing review cycle. In my communications with the toxicological reviewers, it appears that this finding does not indicate impact to the safety, efficacy, or purity of the product.

Facility cleaning in b(4) is performed in accordance with SOP #235762-09, *Cleaning and Sanitization, --b(4)----- Classified Areas Rosia.* The following cleaning agents were appropriately qualified and are approved for use in –b(4)-:

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

Facility cleaning and disinfectant qualifications were reviewed during the inspection; all acceptance criteria were met. Please refer to the EIR for additional detail.

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

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month phase; all acceptance criteria were met. As water was covered during the inspection, please refer to the EIR for additional detail.

The --b(4)---------- is employed in --b(4)----------, and is used to monitor and control temperature, pressure, and %relative humidity in various production areas and cold rooms. The validation of this system as employed in -b(4)-- is documented in the validation summary report for automated systems in fill/finish manufacturing (Attachment 3.2.A.1.2.4.5-2 in the BLA). The qualification of this system appears adequate. An additional review of the -b(4)- was conducted during the inspection. Please refer to the EIR for additional details.

A series of b(4) dedicated air handling units serve the formulation and filling suites in -b(4)--- floor. Clean air is provided to Class b(4) (laminar flow hood devices), --b(4)----- areas. The b(4) HVAC system appears to have been appropriately validated through IQ/OQ/PQ. The IQ consisted of ----------b(4)---. OQ addressed --b(4)------ ----------. Worst-case conditions included ----b(4)--- ----------. All acceptance criteria appear adequate and were met.

Filling – Building b(4)

The vial filling machine/line -b(4)--- (using the --b(4)-- ---------- were qualified via aseptic media fills as documented in Validation Report Media Fill/42/057/--b(4)-----/PVR/00, Approved November 6, 2006, and Validation Report Media Fill/42/059/--b(4)------/PVR/00, respectively. In each qualification, three runs of at least -b(4)---- units were performed under the following worst-case conditions:

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

The alert limit and action limit are --b(4)----------, respectively. An alert (--b(4)----------) occurred during one of three vial fills and a deviation was opened; a fourth run was performed without incident. This deviation and its resolution were reviewed during the inspection. No other alert/action limits were exceeded during either of these qualifications. No objectionable conditions were noted. Please refer to the EIR for additional media fill detail.

Visual Inspection – Building --b(4)------

The MenCWY Liquid -b(4)-- and the MenA Lyo vials are inspected in b(4) rooms --b(4)------ respectively. MenCWY Liquid vials are inspected in b(4), room b(4). These activities are performed in controlled and unclassified areas. The visual inspection machine -b(4)- for the 3mL vials in -b(4)---- was validated as documented in the Performance Qualification Report 42/057/-b(4)-----/PQR/00. This machine was further qualified for 2mL and 3mL vials as documented in PQ Report 42/057/-b(4)----------/PQR/03. These reports were included in the eCTD but the additional b(4)validations were covered

during the inspection. The following table summarizes the visual inspection machines and their corresponding validations:

Drug Product Component	--b(4)----------	-b(4)---	Validation Activities & Documentation
--b(4)----------	-b(4)----	--b(4)----------	---b(4)----------
MenA Lyo Vial	-b(4)----	-b(4)----------	MEN_A_INSP/031/22/--b(4)---/PVR/00
MenCWY Liquid Vial	-b(4)----	-b(4)----------	PQ Report 42/057/-b(4)---/PQR/00 PQ Report 42/057/--b(4)---/PQR/03

Validations for each machine were carried out in a similar manner. Three consecutive runs were performed to demonstrate validation for each machine. Units were inspected manually prior to testing the automated machines. A panel of -b(4)-- rejects was established and defects were qualified through b(4) runs to ensure the cameras could detect all rejects. ----b(4)---------- ---------- There were no deviations. Please refer to the EIR for additional details.

Packaging and Labeling – Building b(4) (3.2.A.1.2.3.2)

Packaging and labeling are performed in b(4), a multi-product facility. These activities are performed in controlled and unclassified areas on a campaign basis only (only one product at a time). Line clearance procedures, to include label reconciliation, were reviewed and verified during the inspection. Any classified areas of b(4) are not associated with Menveo® production. The following products are also packaged and labeled in b(4):

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

Menveo® is packaged into ---------- ---b(4)---------- pre-filled vials -------b(4)----------include a second component, the MenA Lyo Vials. The following table summarizes the associated equipment and validation/qualification activities:

Product Presentation	Equipment	Qualification/Validation
MenCWY Liquid Vials + MenA Lyo Vial	Packaging Line b(4) Packaging Machine -b(4)- Labeling Lines -b(4)---	PQ Report 22/016/-b(4)--/PQR/00
----b(4)---------- ----------	--b(4)----------	--b(4)----------

*No Menveo product had yet been labeled and packaged at the time of the inspection (02/18-27/09).

The packaging machine -b(4)- was validated as documented in Performance Qualification Report 22/016/-b(4)-/PQR/00 for the 3mL and 5mL vials. During this qualification, the machine was challenged for its ability to identify defective units by manually simulating anomalies. A manual inspection was performed at the end of each run. The machine identified all defects in all three runs for each component. The machine also met its false discard criteria. All acceptance criteria were met. The submission did not contain qualification information for Packaging Line -b(4)-, but both lines were covered during the inspection. Please refer to the Packaging and Labeling section of the EIR for additional information.

Storage of Finished Drug Product – Building b(4)

Finished/packaged drug product and finished MenA Lyo (waiting on final labeling/packaging) is stored in Building---b(4)-------- or Building---b(4)---------- until shipment/distribution. Both warehouses employ the b(4) system and materials in these warehouses are controlled as described in the Incoming Materials section of this memorandum.

Shipping

Shipping of finished drug product was reviewed during the inspection.

Issue: The shipping validation for Menveo® final product to the U.S. is incomplete, as noted in Observation #6 of the FDA 483, issued on February 27, 2009.

Resolution: The firm adequately addressed this issue in their response to the 483. The study was subsequently completed on or before May 31, 2009, and the applicable validation reports (20/035/--b(4)----------/00 and ----b(4)----------/20/035/Menveo/PQR/00) were submitted to the BLA file on June 3, 2009 (received by the agency on June 9, 2009). A preliminary review of these documents indicates that a representative material was used to simulate product and appears to be representative of worst-case conditions. The documents indicated that representative product temperature was always maintained at 2-8°C throughout the entire shipment for all three runs. There was one deviation that appears to have been appropriately investigated and was deemed to be the result of improper probe programming. A set of acceptance criteria limits were pre-established for each antigen (some parameters and/or limits vary slightly by antigen) and included --b(4)----------
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All acceptance criteria appear to have been met, although a deeper review will be required to determine how separate criteria for each antigen were established and assessed with the representative product(s). A more detailed review of this shipping study will have to be performed during the next review cycle after the firm responds to the Complete Response letter that will be sent imminently.

Facility Cleaning (3.2.A.1.2.4.3.4.1)

Please note facility cleaning for each building was briefly summarized in the applicable sections of this memorandum. Facility cleaning in b(4) is performed in accordance with SOP #226737-05, *Sanitization of controlled and classified areas, b(4)*, effective February 12, 2009, approved February 11, 2009. Facility cleaning in b(4) is performed in accordance with SOP #235762-09, *Cleaning and Sanitization, b(4) and b(4) Classified Areas Rosia*, effective November 26, 2008, approved November 18, 2008. B-5

employs similar procedures in a separate document. All procedures prescribe the same disinfectants, buckets, and mops. Collective classified areas of both buildings include Class --b(4)----------. The following table describes the disinfectants and their respective contact times, in accordance with the aforementioned procedures:

Disinfectant	Minimum Contact Time	Specified Use
--b(4)----------	--b(4)------	---b(4)----------
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--b(4)----------	--b(4)------	--b(4)-- ----------
--b(4)----------	--b(4)------	--b(4)-- ----------

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

Procedures defined in the aforementioned SOPs require high to low cleaning starting with the cleanest areas first, progressing to the most dirty (floors). Other measures taken to ensure cleanliness include a ----------b(4)----------

Disinfectants are validated through in vitro and efficacy testing. --b(4)---------- The following table describes the acceptance criteria of both tests, all of which were met:

[b(4)]

The following table describes the general cleaning schedule applied throughout all of the Menveo® manufacturing buildings in Rosia:

[b (4)]

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

[b(4)]

Equipment Cleaning

Equipment cleaning rigor is partly dependent upon dedicated vs. shared, and contamination risk. The overall approach also considers the similarity of the physiochemical characteristics of the different intermediates.

Issue: As documented in Observation #5 on the FDA 483 (issued February 27, 2009), "*a risk assessment has not been performed and documented to support the sanitization program.*" During the inspection I discovered that Novartis had an undocumented sanitization program in that some equipment and vessels were validated for sanitization, and other equipment and vessels were validated for sterilization.

Resolution: Novartis has since responded to this observation, and they have produced a rationale and risk assessment to support their approach. I found their response adequate and recommend that the new risk assessment be reviewed during the next site inspection.

Equipment cleaning was referenced in eCTD sections 3.2.A.1.3.2.1 and 3.2.A.1.2.1.2 for the -b(4)---- and Rosia sites, respectively. Additional information is required to fully assess equipment cleaning validation and this deficiency will be included as an information request either in the Complete Response letter (expected to be sent prior to the action due date of June 29, 2009), or as a separate request. Requested information will include a request for clarity of the –b(4)-acceptance criterion of -b(4)-- (shared equipment) and -b(4)- (dedicated equipment) of product/detergent carryover. The cleaning validation summaries provided in the --b(4)-- section were insufficient for a thorough review, and therefore the full reports will also be requested in the CR letter, given the -b(4)------ inspection has been waived.

Equipment cleaning was further reviewed during the inspection for each applicable equipment category, e.g., columns, filters, centrifuges, CIP, etc. I also reviewed a few manual cleaning procedures, to include the -b(4)----- centrifuge used in the --b(4)----------

Issue: As noted in observation #9 of the FDA 483, this particular cleaning procedure was inadequate in that it allows for the potential of cross-contamination with residual product carryover from shared utensils used in a --b(4)----------. This ----b(4)----------. It is important to note that the centrifuge ----b(4)----------. The applicable cleaning procedure, SOP# 231206, *Cleaning of the --b(4)----------*, requires the operator to disassemble the centrifuge into its various parts, but these parts were not identified anywhere in the procedure. Furthermore, not all manual cleaning operators are re-qualified on any periodic basis.

Resolution: Novartis has since responded to the FDA 483, and have indicated that SOP #231206 has been updated to provide for and identify dedicated cleaning utensils where possible, for dedicated equipment. The revised procedure also clearly identifies each of the centrifuge parts. Lastly, Novartis intends to make improvements to their manual cleaning training module, and will establish a periodic requalification interval. I am satisfied with their response to this issue, and recommend that it be followed up on during the next site inspection.

Please refer to the EIR in each equipment category for additional information.

Computer Systems

Novartis employs the following computer and automated systems in support of Menveo® manufacturing:

- Rosia Alarm System: Controls temperature/alarms for --b(4)----------
- --b(4)---------- Key equipment is connected to b(4)w/ alarm capabilities in ---------b(4)---. It is also used to monitor and control HVAC systems and controlled environments for temperature, relative humidity, and pressure. This system provides alarm notification, data trends, and data archive.
- b(4) Controls process automation for the glycoconjugate manufacturing in b(4)
- --b(4)---------- controls the ---b(4)--- for glycoconjugate manufacturing
- Centralized Building Monitoring System: Monitors cold storage, utilities, and other critical service equipment. This system provides off-site notification.

Each section of this memorandum briefly describes the applicable computer systems used in the respective manufacturing areas. Please also refer to the EIR for additional computer systems detail.

Environmental Monitoring

The environmental monitoring program for all critical and classified areas complies with FDA, European Union, and ISO. The EM program is carried out in accordance with SOP #201430, *General Procedure for Environmental Control*. The firm was cited during a previous inspection (February 4-11, 2008) for not following their own procedure to conduct active air monitoring during set-up. EM was observed during the Menveo® PAI, and no objectionable conditions were found.

Review History

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