Summary Basis for Regulatory Action (SBRA)

Date	February 16, 2010
From	Willie F. Vann, Ph.D., Chair
Subject	Summary Basis for Regulatory Action
BLA#	125300/0
Applicant	Novartis Vaccines and Diagnostics, Inc.
Date of Submission	29 August 2008
Proprietary Name	Menveo®
Dosage Forms	After reconstitution a 0.5 mL solution.
Proposed Indication	Active immunization for the prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, Y and W-135 when administered to individuals 11 through 55 years of age.
Recommended Action	Approval
Signatory Authority Action	*Office Signatory Authority:* *I concur with the summary review* *I concur with the summary review and include a separate review or addendum to add further analysis* *I do not concur with the summary review and include a separate review or addendum.*

Table 1: Review documents used in compiling this SBR**A**

Review Category	**Reviewer--date of review**
Clinical Review	Margaret Bash, MD – 2 February, 2010
Statistical Review	Barbara Krasnicka, Ph.D. 27 January, 2010
Pharmacovigilance Review	David Menschik, M.D. – 13 January, 2009 David Martin – 17 December. 2009 and 25 January, 2010
CMC Review	Daron Freedberg Ph.D. - 11 February, 2010 Robert Lee, Ph.D. - 3 February, 2010 Milan Blake, Ph.D. - serological assays, 12 February, 2010
Product Testing/DPQ Review	Rajesh Gupta, PhD - 27 January, 2010
Facilities Review	Nicole Trudel - 24 June, 2009 Joseph George - 2 June, 2009, 22 June, 2009, 24 June 2009, 22 January, 2010, and 26 January, 2010
Bioresearch Monitoring	Patricia Holobaugh/Janet White - 12 June, 2009
Advisory Committee Transcript	N/A
Container and Labeling	Catherine Miller – 27 February, 2009 Daphne Stewart – 23 December, 2009
Proprietary name review	Catherine Miller - 29 December, 2009
Pharmacology/Toxicology	Nabil Al-Hamadi – 9 February, 2010 Marion Gruber - 1 May, 2009

1. Introduction

Biologics License Application (BLA) STN 125300 for Menveo® (Meningococcal (Groups A, C, W-135 and Y) CRM197 Oligosaccharide Conjugate (MenACWY)) vaccine was submitted on 29 August 2008 by Novartis Vaccines and Diagnostics S.r.L. Bellaria-Rosia, 53018 Sovicille, -b(4)--, Italy (Novartis). The applicant seeks licensure for active immunization (by a single intramuscular administration) of individuals 11 through 55 years of age for prevention of invasive meningococcal disease caused by *Neisseria meningitidis*, serogroups A, C, W-135 and Y, bacteria.

2. Background

The original submission was reviewed and a number of deficiencies related to chemistry, manufacturing, and controls (CMC) and clinical issues were found. These CMC deficiencies included process validation, method validation, and appropriateness of analytical methods and specifications. Process steps involving ----------b(4)------ were not properly validated. There was insufficient data to support time limits for critical manufacturing steps. Several process and release assays were not properly validated. The assay validation issues were varied and included, but were not limited to: appropriate accuracy studies, sample matrix, and validation of ---b(4)---------- ---------- The specifications for release test were not appropriately justified.

Major clinical issues identified included inconsistencies observed in the designation of severity and relatedness of adverse events, possible unblinding at two study sites of one multicenter trial and the potential for immunogenicity subset designations to unblind some sera. A complete response (CR) letter including these issues was sent to the sponsor on 25 June 2009. Novartis submitted a response to CBER on 21 August 2009. The response adequately addressed the deficiencies.

3. Chemistry Manufacturing and Controls (CMC)

Product Summary:

Meningococcal (Groups A, C, Y and W-135) Oligosaccharide Diphtheria CRM_{197} Conjugate Vaccine (tradename Menveo®) consists of four drug substances, each composed of a Meningococcal capsular oligosaccharide covalently attached to the genetically modified Diphtheria Toxin CRM197 protein. 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).

Menveo® is packaged as two components consisting of *Neisseria meningitidis* serogroup A oligosaccharide-CRM_{197} conjugate in lyophilized form that is to be reconstituted with a mixture of *Neisseria meningitidis* serogroup C, Y, and W-135 oligosaccharide-CRM_{197} conjugates in liquid form. The drug substances are manufactured at Novartis Vaccines and Diagnostics S.r.l. Bellaria-Rosia, 53018 Sovicille, -b(4)- Italy. *Neisseria meningitidis* serogroup A oligosaccharide-CRM_{197} conjugate is formulated, filled, and lyophilized at Novartis Vaccines and Diagnostics --b(4)-- ----------. The Drug Product consisting of both components is packaged, labeled and shipped at the Rosia site. A prelicense inspection of the Rosia site at Bellaria-Rosia, 53018 Sovicille, -(b)(4)-, Italy was conducted on 18-27 February 2009. Inspection of the --b(4)---------- site was waived because the manufacturing process (formulation and fill) at this site is not significantly different from that of other approved products produced in the -b(4)------facility. The same type of equipment is used and product contact equipment is dedicated. Please refer to the inspection wavier dated 7 July 2009 for more detail.

Drug Substance:
There are four Drug Substances contained in Menveo®, each prepared from a specific capsular polysaccharide isolated from either *N. meningitidis* Groups A, C, Y, or W-135.

- *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.

The major process intermediates 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}.

The capsular polysaccharides used to prepare these Drug substances have the following structures:

Polysaccharide	**Repeating Structure**
MenA	α(1,6)N-acetylmannosamine
MenC	α(2,9)N-acetylneuraminic acid
MenY	→4)-N-acetylneuraminic acid(7/9OAcetyl)-α-(2→6)-glucose α-(1→.
MenW-135	→4)Nacetylneuraminic acid(7/9OAcetyl)-α-(2→6)-galactose-α-(1→].

--b(4)--- --

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

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

Characterization – The Drug substances were analyzed by appropriate and sensitive methods. For a detailed evaluation of the methods used for assay of the Drug Substance, please refer to the CMC review memorandum, 20 January 2010, by the Division of Product Quality (DPQ) reviewer. Review of these data suggests that the manufacturing process is consistent and results in a conjugate with consistent properties such as ------------------------------------(b)(4)------------------------------------. However, Novartis proposed to ---b(4)---. Novartis proposed -----b(4)--- because it was their opinion that consistency has been demonstrated. For example, in the Men Y-CRM Conjugate, Justification of Specification (3.2.S.4.5), page 12, the --b(4)---------------------------- (SOP 202606) is listed as " --b(4)-- ---. This led us to recommend in the CR letter that ----b(4)--

-- ----------. Novartis satisfactorily committed in a subsequent amendment to assaying for sialic acid.

Drug Product:

Menveo® is presented as a multiple dose package consisting of 5 vials containing the MenA lyophilized and 5 vials containing the MenCWY Liquid

The contents of the MenA lyophilized vial are reconstituted with the contents of the MenCWY Liquid vial in order to administer 0.5 mL of reconstituted vaccine (MenACWY). The composition of these components is given in the tables below:

Composition of MenCWY Liquid Conjugate Component

Name of Ingredient	**Unit and/or Percentage Formula (Dose 0.5 ml)**	**Function**
MenC-CRM	5 µg MenC oligosaccharide --b(4)----- CRM197	--b(4)-----
MenY-CRM	5 µg MenY oligosaccharide --b(4)----- CRM197	--b(4)-----
MenW-CRM	5 µg MenW-135 oligosaccharide --b(4)----- CRM197	--b(4)-----
Excipients		
--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)----------	--b(4)------

Composition of MenA Lyophilized Conjugate Component

Name of Ingredient	**Unit and/or Percentage Formula (Dose 0.5 mL)**	**Function**
MenA-CRM	10 µg MenA oligosaccharide --b(4)----- CRM_{197}	--b(4)----------
Excipients		
--b(4)---------- ----------	-b(4)-----	---b(4)----------
--b(4)-----	--b(4)------	--b(4)---------- ---------- ----------

Control of Drug Product:

Specifications for release of Menveo® final bulk, the important bulk intermediates, and final container vaccine are detailed in the tables below. Final specifications were established using information from the testing of development and commercial batches and through communications with Novartis.

125300 Meningococcal ACWY Conjugate Vaccine
Specifications

Specifications for tests on packing lot	
Test	**Specification**
Identity for MenC-CRM	--b(4)-------
Identity for Men A-CRM, MenW-CRM and MenY-CRM	--b(4)-------

Specifications for tests on Purified MenA polysaccharide bulk	
Test	**Specification**
--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)-------
--b(4)----------	--b(4)-------

Specifications for tests on purified protein CRM 197 bulk	
Test	**Specification**
--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)-------
--b(4)----------	--b(4)-------
--b(4)----------	--b(4)-------

Specifications on MenA-CRM Conjugate concentrated bulk	
Test	**Specification**
--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)-------
--b(4)----------	--b(4)-------
--b(4)----------	--b(4)-------
--b(4)----------	--b(4)-------
--b(4)----------	--b(4)-------
--b(4)----------	--b(4)-------
--b(4)----------	--b(4)-------

Specifications on MenA-CRM Final Bulk	
Test	**Specification**
Sterility	Sterile

Specifications for tests on Men C polysaccharide bulk	
Test	**Specification**
--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)-------
--b(4)----------	--b(4)-------

Specifications for tests on Men C-CRM conjugate concentrated bulk	
Test	**Specification**
--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)-------

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

Specifications for tests on Men W polysaccharide bulk	
Test	**Specification**
----------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)------
----------b(4)----------	--b(4)------

Specifications for tests on Men W-CRM conjugate concentrated bulk	
Test	**Specification**
----------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)------
----------b(4)----------	--b(4)------
----------b(4)----------	--b(4)------
----------b(4)----------	--b(4)------
----------b(4)----------	--b(4)------
----------b(4)----------	--b(4)------
----------b(4)----------	--b(4)------

Specifications for tests on Men Y polysaccharide bulk	
Test	**Specification**
----------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)------

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

Specifications for tests on MenY-CRM Conjugate Concentrated Bulk	
Test	**Specification**
--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)------
--b(4)----------	--b(4)------
--b(4)----------	--b(4)------
--b(4)----------	--b(4)------
--b(4)----------	--b(4)------
--b(4)----------	--b(4)------

Specifications on Men CWY conjugate final bulk	
Test	**Specification**
Sterility	Sterile

Specifications for tests on Final Container MenA Lyophilized	
Test	**Specification**
Identity --b(4)------	--b(4)------
Residual moisture by --b(4)------	--b(4)------
Protein content by --b(4)------	--b(4)------
Appearance of lyophilized plug by visual examination	--b(4)------
Appearance after reconstitution by visual examination	--b(4)----------
--b(4)------	--b(4)------
--b(4)----------	--b(4)------
--b(4)----------	--b(4)------
----b(4)----------	--b(4)------
General Safety Test -----b(4)----------	--b(4)------
Endotoxin ----------(b)(4)----------	--b(4)------
Sterility	--b(4)------

Specifications for tests on Men CWY Final Container (Fill Vaccine)	
Test	**Specification**
Identity for MenC-CRM	--b(4)------
Identity for MenW-CRM and MenY-CRM	--b(4)------

Appearance by visual examination	--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)----------	--b(4)------
----b(4)----------	--b(4)------
General Safety Test	--b(4)------
Endotoxin	--b(4)------
Sterility	--b(4)------
Volume	--b(4)------

Analytical procedures

The data submitted to support the analytical methods used for testing of Drug Substance (DS) and Drug Product (DP) of Meningococcal ACWY Conjugate Vaccine, Menveo®, and specifications proposed for release of DS and DP were reviewed. A number of issues with regard to analytical methods and adequacy of analytical method validations and proposed specifications were found in the original submission. A complete response letter including these issues was sent to sponsor on 25 June 2009. The sponsor addressed all the issues related to analytical methods, method validations, and specifications in amendment 0.15 to the BLA.

Refer to product testing/DPQ review memorandum, 27 January 2010, for detailed information on analytical procedures.

Date of Manufacture:

The date of manufacture is defined as the date of initiation of formulation of each component of the drug product, i.e., Meningococcal Serogroups C, Y, and W-135 liquid conjugate component plus Meningococcal Serogroup A Oligosaccharide Diphtheria CRM_{197} conjugate component. The expiration date for the packaged product, Meningococcal Serogroups C, Y, and W-135 liquid conjugate component plus Meningococcal Serogroup A Oligosaccharide Diphtheria CRM_{197} conjugate component, shall be dependent on the shortest expiration date of either component.

Stability

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

MenCWY Liquid

During process development, several lots were used to demonstrate stability of MenCWY Liquid. 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 (syringe or 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 at 2 to 8°C.

MenA-CRM$_{197}$ lyophilized powder

Novartis has an ongoing stability study to support a --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 ----------(b)(4)----------, thus 36 month dating is recommended by CBER for the MenA-CRM$_{197}$ lyophilized powder. --b(4)--- ----------

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 of reconstituted product

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

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

The proposed shelf life of the reconstituted vaccine is not more than -b(4)---- when stored at --b(4)---------- content and percentage of ---b(4)---------- were selected as key parameters to evaluate any possible effect during the short-term storage. Moreover, --b(4)---------- were also monitored. Results with reconstituted samples of MenACWY vaccine stored for --b(4)--- at both -b(4)----------and for --b(4)---------- did not change from values obtained at time 0.

Lot Release

For routine lot release, the firm will submit samples and a Lot Release Protocol for each final container lot to CBER. A testing plan was developed by DPQ and accepted by the review committee.

The firm submitted b(4) launch lots in support of approval:

Matching List		Packing Lot number
MenA Lyo Component	MenCWY Liquid Component	
027011	090901	100001
028011	090901	100002
028011	091001	100003
029011	091001	100004
029011	091101	100005

These lots were tested at CBER for:

Sterility
Endotoxin
Identity
pH
Moisture (MenA lyo only)

In addition, bulk lots of Drug Substance were submitted for testing. These lots were used to prepare the launch lots and are listed below:
MenA-CRM Conjugate
-b(4)-
-b(4)-
-b(4)-

MenC-CRM Conjugate
-b(4)-
-b(4)-
-b(4)-

MenW-CRM Conjugate
-b(4)-
-b(4)-
-b(4)-

MenY-CRM Conjugate
-b(4)-

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

These conjugates were assayed for the following:

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

All bulk and final container lots tested were within specifications.

Clinical Serology Assays

Novartis Vaccines and Diagnostics (NVD) submitted as part of their BLA a validation report, Document No. 231439-02, for a serum bactericidal assay. The assay determines the level of ---b(4)----------against *Neisseria meningitidis* serogroups A, C, W-135, and Y (hSBA validation report) for -b(4)- Meningococcal ACWY Conjugate Vaccine (MenACWY). This validation report was previously reviewed under BB-IND -b(4)--- with minor changes.

The data presented in the validation report Doc. No. 231439-02 demonstrates that the assay as performed using SOP No. 222582 meets criteria for repeatability, intermediate precision, linearity, specificity, and detection as well, as quantitation limits.

Facilities Review

An announced, Pre-License Inspection of Novartis Vaccines and Diagnostics S.r.l. was conducted in Rosia, Italy (FEI #3006738517) for their new Meningococcal ACWY Conjugate Vaccine, Menveo®. This was a comprehensive inspection covering quality, production, facility and equipment, materials, packaging and labeling, and laboratory control systems. The inspection was conducted from 18 February 2009 (Wednesday) to 27 February 2009 (Friday). Throughout the course of the inspection, several objectionable conditions were observed during the facility walk-through and noted during document review. A brief summary of the significant objectionable conditions observed during the inspection include:

- Inadequate process validation;
- Time limits for critical manufacturing steps are not always established;
- Deviation management procedures are not always followed;
- Not all analytical procedures are adequately validated;
- There is no rationale or justification for the sanitization program;
- Shipping validation has not been completed;
- Hold times of less than --b(4)--- have not been validated;
- Qualifications of ---------(b)(4)--------- storage vessels have not been completed;
- Manual cleaning procedures are inadequate.

At the conclusion of the inspection on 27 February 2009, a Form FDA-483 containing eleven observations was issued to Carmelo D'Ancona, Head of Technical Operations, Italy. These issues are fully detailed in the establishment inspection report (EIR) in Section 12, Objectionable Conditions and Management's Response. The firm has provided acceptable responses to each observation noted on the Form 483. The firm's proposal for addressing inadequate process validation was acceptable. Review of data obtained from re-validation studies were evaluated by the BLA review committee and found acceptable.

For further details on the inspection please refer to the following documents:

- Establishment Inspection Report dated 24 June, 2009
- Facilities Review Memo of Nicole Trudel dated 29 June 2009
- Facilities Review Memo of Joseph George dated 29 June 2009

A Comparability Protocol (CP) for filling MenCWY Liquid on Novartis -b(4)-- filling line in Rosia, Italy was included in the original BLA for Menveo®. Review of the original CP, as found in the BLA, can be found in the Memo by Joseph George dated 24 June 2009. An Information Request was sent to Novartis on 21 May 2009. The firm provided a response on 22 June and 21 August 2009. Approval of this CP for the --b(4)---------- for use in Menveo® filling is recommended. The implementation supplement should be categorized as a CBE-30 when submitted.

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, the waiver is acceptable. This assessment is also documented in the Environmental Analysis Assessment review memorandum by Joseph George.

4. Non-clinical/Toxicology

A single and a multiple dose intramuscular study were performed in ---b(4)---------- rabbits with meningitis vaccine formulations to evaluate the possible toxicological effects of Menveo®. The test articles in this study were:

Test article batch/lot:
Monovalent meningococcal A antigen lyophilized (MenA): ChB552001011
Trivalent meningococcal CWY antigens ---b(4)---------- (MenCWYb(4)): MenCWYPO1V
Trivalent meningococcal CWY antigens --b(4)---------- (MenCWYb(4)):

MenCWYH01V

In this single (40 µg/0.5 mL dose) and repeated (five 40 µg/0.5 mL dose at two weeks interval) dose toxicology study, b(4) rabbits were treated with either control or test articles. Control or test article were administered via intramuscular (gluteal muscle of the hind limb) injection on study days (SD's) 0, 14, 28, 42, and 56. Terminal sacrifice necropsies were conducted on SD's 2 and 58 for single and repeated dose studies, respectively. Recovery sacrifice necropsies were conducted on SD's 14 and 70 for single and repeated dose studies, respectively.

Based on the overall findings in this study, it can be concluded that in -b(4)--- rabbits single or repeated intramuscular administration of Men ACYW vaccine had no adverse effects in terms of systemic toxicity and local tolerance at the dose level of 40 µg antigen. Immunology performed in this study verified that an active dose was administered.

GLP study deviations or amendments:
No significant deviations or amendments were recorded that influenced the quality, integrity, or interpretation of the results.

Conclusions:
Based on nonclinical toxicity assessments of this study, there are no significant safety issues to preclude approval of this BLA. For further details on this study, please refer to the review memo on nonclinical toxicity dated 9 February 2009.

Reproductive Toxicology Studies
To evaluate the reproductive and developmental toxicity potential of Menveo®, -b(4)- rabbits were dosed 3 x prior to mating and again on gestation days 7 and 20 either with Menveo®, 0.5 ml, I.M., 25 µg antigen, or saline control. Animals underwent Caesarean section or were allowed to rear their offspring (27 rabbits/group). Treatment of animals with Menveo® did not induce vaccine related maternal death or abortion. Clinical signs during the pre-mating, gestation and lactation period, body weights and feed consumptions were comparable across treatment groups. Mating and fertility indices as well as Caesarean-sectioning, natural delivery and litter parameters were unaffected by treatment with Menveo®. There appeared to be no treatment related effects on fetal viability, fetal body weight, sex, gross external or soft tissue or skeletal examinations. F1 pup viability, body weight, sex, reflex and physical development were not affected by treatment with the vaccine.

Conclusion:
In summary, under the conditions of the study, Menveo® did not affect embryo-fetal pre-and postnatal development and did not exert teratogenic effects. Based on these results, the labeling should state pregnancy category B.

5. Clinical Pharmacology

The mode of action of this vaccine is to induce bactericidal antibody against *Neisseria meningitidis* serogroups A,C,Y, and W-135. *Neisseria meningitidis* is a gram-negative diplococcus that causes life-threatening invasive disease such as meningitis and sepsis. Globally, 5 serogroups, A, B, C, Y and W-135, cause almost all invasive meningococcal infections. The majority of meningococcal infections in the U.S. are caused by serogroups B, C, and Y. Vaccination with Menveo® has been demonstrated to lead to the production of bactericidal antibodies directed against the capsular polysaccharides of serogroups A, C, Y and W-135.

6. Clinical/ Statistical-Efficacy

Safety and immunogenicity data were submitted in support of Menveo®. This is the first licensing application for this vaccine worldwide although Novartis has developed a monovalent serogroup C conjugate vaccine Menjugate®, using similar manufacturing methods, which is currently licensed in other countries, including the UK, Canada, and Australia. Currently, two meningococcal vaccines are licensed for the prevention of disease caused by *Neisseria meningitidis* serogroups A, C, W-135, Y in the U.S. Menomune® (Sanofi Pasteur Inc.) is a quadrivalent polysaccharide vaccine and Menactra® (Sanofi Pasteur Inc,) is a quadrivalent polysaccharide-protein conjugate vaccine. Invasive meningococcal disease occurs in the U.S at a rate of 0.5 to 1.1/100,000 (1), and the relatively low prevalence of disease combined with the availability of currently licensed meningococcal vaccines precludes the conduct of studies to evaluate directly the efficacy of new meningococcal vaccines in prevention of clinical invasive disease. The approach used to evaluate safety and effectiveness of Menveo® to support licensure in the U.S. was to compare safety outcomes and serum bactericidal antibody responses after vaccination in comparison to the U.S. licensed vaccine, Menactra®.

The bactericidal activity of serum from vaccine recipients is accepted by the FDA as an appropriate surrogate for evaluating vaccine effectiveness of meningococcal vaccines because complement mediated bacterial killing by bactericidal antibodies has been shown to be the primary mechanism of protection against meningococcal disease. In this application, bactericidal assays using human complement [human serum bactericidal antibody (hSBA)] were used. Licensure of serogroup A and serogroup C meningococcal polysaccharide vaccines was originally supported by demonstrated clinical efficacy in preventing invasive meningococcal disease. The quadrivalent polysaccharide vaccine (Menomune®) contains, in addition to serogroups A and C, serogroups Y and W-135 polysaccharides that were evaluated on the basis of demonstrating four-fold rise in SBA using exogenous rabbit complement (rSBA). Menactra® was licensed in 2005 on the basis of immunologic (SBA) non-inferiority to Menomune®. The SBA used an exogenous complement source that was either human (proportion with hSBA titer $\geq$1:8, 2-10 year old age group) or, when correlated to hSBA, baby rabbit complement (proportion with 4 fold rise in rSBA titer, 11-55 year old age group). The clinical studies of Menveo® were intended to evaluate immunogenicity and safety in comparison to US licensed meningococcal vaccines.

<u>Statistical considerations</u>

The statistical review is based on the applicant's submissions listed in Section 2.3 of the BLA.

Brief overview of clinical studies

The license application for use of MenACWY vaccine for subjects 11 to 55 years of age included safety and immunogenicity data obtained from three pivotal clinical studies and two supplemental clinical studies. A summary of the studies is given in the table below.

Summary of Clinical Studies

Study Protocol	Primary Objectives	Study Population Age (years)	Total # of Subjects	Study Design	Test Product	# of subjects Exposed (at Visit 1)
Pivotal Studies						
V59P13	Safety +	11-55	3432	Randomized Active-Controlled	MenACWY	2649
USA	Lot consistency +	11-18	1575	Multi-center		
	Immunogenicity	11-55	3432	Phase III	Menactra	875
V59P18	Safety +			Randomized, Open-Label	MenACWY +Tdap+HPV	540
Costa Rica	Immune Response of	11-18	1620	Active-Controllled		
	MenACWY with or			One-center	MenACWY then Tdap	541
	without Tdap and HPV			Phase III	Tdap then MenACWY	539
V59P17				Observer-Blind, Randomized	MenACWY	1817
Colombia	Safety +	19-55	2815	Active-Controlled		
Argentina	(Immunogenicity)	56-65		Multi-center	Menactra	889
				Phase III	Menomune	109
Supplemental Studies						
V59P6				Single-Blind, Randomized	MenACWY IM	164
USA	Safety +	11-17	524	Active-Controlled	MenACWY IM	151
	Immunogenicity			Phase III, Multi-center	Menomune	209
V59P11	Safety +			Observer-Blind, Randomized	MenACWY IM with	359
Italy	Immune Response of	11-17	524	Active-Controlled	Boostrix	
	MenACWY with or			Phase III	MenACWY IM	357
	without Boostrix			Multi-center	Boostri	353

(b)(4)

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(b)(4)

The objective of the clinical studies supporting this BLA was to provide evidence that MenACWY vaccine supports an indication for "*active immunization of individuals 11 through 55 years of age to prevent invasive meningococcal disease caused by Neisseria meningitidis serogroups A, C, W-135 and Y.*" With regard to immunogenicity and safety of MenACWY, the applicant's approach was to demonstrate non-inferiority of MenACWY as compared to US licensed vaccines, Menactra® and Menomune®.

The statistical evaluation of the data in the submission was based on three pivotal and two supplemental studies mentioned above. In the case of Study V59P13, all three primary immunogenicity objectives (one lot-to lot-consistency and two non-inferiority hypotheses for two age groups) were met. Among participants aged 11-18 years, the seroresponse rates for 3 vaccine lots revealed some statistical differences for each serogroup, particularly for W135 (lot A 74%, lot B 80%, lot C 70%), although they were not consistently high or low for any single lot. Similar remarks are applicable to percentages of participants with hSBA titer >1:8.

Certain irregularities were considered in the interpretation of the V59P13 data:

1. Without pre-specification in the study protocol of the sample-size re-estimation, the numbers of subjects in the immunogenicity subsets were increased 6 months after finishing the study enrollment.
2. After the special second sample selection, the data structure of the first randomization for the immunogenicity testing was not retained for serogroups W and Y. For these groups, the effective randomization ratio for MenACWY vs. Menactra was 3:5:1 instead of the pre-specified 3:1.
3. Immunogenicity populations for serogroups W and Y were slightly younger for the MenACWY group (mean: 22, standard deviation: 12) than for the Menactra group (mean: 27, standard deviation: 14).
4. Each serogroup had its own subset population. Thus, immunogenicity hypotheses were tested on different datasets that contained different numbers of subjects and sometimes different subjects.
5. The vaccine group assignment in two study sites was unblinded prematurely. However, statistical testing of a possible influence of these two sites on the primary endpoint results was performed by the applicant and the results revealed that outcomes from these two centers did not have a noticeable influence on the clinical study outcomes.

The second pivotal study, V59P18, was done in one center in Costa Rica. The study population consisted of healthy adolescents 11 to 18 years of age. Subjects in the study received three types of vaccines: MenACWY, Tdap and human papillomavirus vaccine, GARDASIL®. Based on a pre-BLA agreement between the applicant and CBER, the HPV safety and immunogenicity data for girls was planned to be reviewed as a separate BLA supplement (at the time, the use of GARDASIL® was not approved for boys). Therefore, for study V59P18, only immune responses to MenACWY when given sequentially before or after Tdap were assessed by the reviewer. The assessment showed that the co-primary immunogenicity objective #3 (non-inferiority immunogenicity hypotheses for sequential administration of MenACWY following Tdap based on seroresponse) was not met for one of the serogroups. Thus, the goal of rejecting all three co-primary hypotheses was not met.

Clinical Studies Effectiveness Data

Immunogenicity and Inferred Effectiveness

Pivotal immunogenicity data to support lot consistency and non-inferiority to Menactra® were provided in study V59P13. Immunogenicity was evaluated on subsets of the per protocol population for each serogroup. Laboratory assessments were blind to immunization group, and differences in subset populations were evaluated during the review, but were not assessed as having a meaningful impact on the immunogenicity endpoints. All primary end-points comparing pairwise the three lots of Menveo® for the four serogroups were met (equivalence based on hSBA GMTs for lot consistency), thus providing clinical evidence supporting consistency of manufacture. Immunogenicity data for the three lots were therefore combined for noninferiority comparisons to Menactra®.

Effectiveness of Menveo® was inferred from immunogenicity as assessed by evaluation of serum bactericidal activity (hSBA) in response to immunization with Menveo® compared to the currently licensed meningococcal conjugate vaccine, Menactra®. Non-inferiority of hSBA responses to Menveo® compared to Menactra® was shown for all four serogroups for individuals 11-18 years of age and 19 – 55 years of age using a composite endpoint of seroresponse rates, defined as follows: for subjects with hSBA titer <1:4 at baseline, seroresponse was a postvaccination hSBA titer ≥ 1:8; for subjects with hSBA titer ≥ 1:4 at baseline, seroresponse was a post vaccination hSBA titer of at least 4 times the baseline titer.

All secondary end-points (based on seroresponse, geometric mean titer [GMT] and % ≥1:8 in 11-55 year age groups) also met pre-specified non-inferiority criteria for each serogroup. Additional exploratory analyses were requested during the review, such as analysis of non-inferiority using non-interpolated titers, and an analysis excluding two study sites that may have been unblinded to study group. Exploratory analyses also indicated satisfactory hSBA responses in comparison to Menactra®.

Criteria for superior immune responses indicated in the clinical protocol and analysis plan required that (1) non-inferiority was achieved and (2) that the lower limit of the 2 sided 95% confidence interval around the difference in proportions (Menveo® – Menactra) or ratio of GMTs (Menveo® /Menactra) was greater than 0% or 1.0 respectively. The clinical significance of statistically significantly higher immune responses is unknown as there are no clinical data demonstrating differences in meningococcal disease prevention due to higher post-immunization immune responses. Therefore explicit or implicit superiority claims based on the immunogenicity data reviewed were not considered by the review team as appropriate for labeling purposes.

Concomitant administration of Menveo® with Boostrix® and GARDASIL® did not cause interference between the immune response of Menveo®, tetanus, diphtheria or pertussis toxin. The geometric mean antibody titers (GMTs) to two pertussis antigens, FHA and pertactin, were lower in subjects in the concomitant administration group than in those that received Boostrix® alone. This assessment was conducted in the context of GARDASIL® also administered to the concomitant group; therefore, data were inconclusive as to the effect of Menveo® on the immune responses to pertussis antigens. Data were also insufficient to evaluate vaccine interactions when Menveo® was administered one month before or one month following Boostrix®. Further evaluation of the effect of Menveo® on U.S. recommended adolescent vaccines will be undertaken as a postmarketing commitment by Novartis.

Reports of Potential Vaccination Failures

There were no reports of serious adverse events interpretable as potential vaccine failures.

Bioresearch Monitoring

The bioresearch monitoring inspections of four clinical sites did not reveal problems that impact the data submitted in the application.

7. Safety

Clinical Studies Safety Data

The total safety database for the proposed formulation and indicated age group consisted of 6185 subjects from 5 studies. These studies enrolled a total of 3579 adolescents 11 to 18 years of age, and 2606 adults 19 to 55 years of age from three pivotal (V59P13, V59P17, V59P18) and two supportive studies (V59P6 and V59P11). For comparator vaccines, 1757 subjects provided safety data for Menactra®, 209 provided safety data for Menomune®, and 892 provided safety data for Tdap from vaccine co-administration studies. Two pivotal randomized blinded, controlled safety studies provided comparative safety data for the indication sought.

In study V59P13, a multi-center, observer-blind, randomized study in the United States, 2649 Menveo® subjects were evaluable for safety. In study V59P17, a multi-center, observer- blind randomized study in Columbia and Argentina, 1588 Menveo® subjects were evaluable for safety. The planned post vaccination period for each subject in both studies was 180 days.

In V59P18, a single center open label, multiple vaccination study in Costa Rica, safety of Menveo® in 1620 healthy adolescents 11 to 18 years of age administered either alone or concomitantly with combined tetanus, reduced diphtheria, and acellular pertussis (Tdap) vaccine (GlaxoSmithKline [GSK], US-licensed Boostrix®), and quadrivalent human papillomavirus [type 6, 11, 16, 18] (HPV) recombinant vaccine (Merck & Co.,GARDASIL®) was evaluated. Data through 2 months following vaccination were evaluated for safety.

The safety profile of Menveo® in each individual study was similar to that observed by combining safety data across studies. Local and systemic reactogenicity occurred in a similar percent of subjects immunized with Menveo® or the comparator vaccine. Severe reactions occurred infrequently. Adverse events were more frequent in females and less common in the 35-55 year old age group. Geographic distribution, which largely corresponded to racial demographics (primarily Caucasian in US studies and Hispanic in South/Central American studies), did not affect AE profiles.

Solicited adverse reactions in the primary U.S safety study:

The percentages of subjects reporting all solicited AEs in the Menveo® group and in the Menactra® group were: solicited AEs: 62% vs. 67%; local solicited AEs: 48% vs. 53%; systemic AEs 41% vs. 40%, respectively. The solicited events “use of analgesic/antipyretic medication” and “stayed at home due to vaccination” occurred in 21% of both vaccine groups.

Pain was the most frequently reported local solicited AE. While local AEs were reported in slightly fewer Menveo® recipients, severe local reactions were reported more frequently compared with Menactra® (overall, 4% vs. 2%, respectively). The median duration of all severe local reactions were similar in the Menveo® and Menactra® groups (2 days for severe pain in both vaccine groups; 4 days

for erythema >50mm in both vaccine groups and 3 and 4 days in the Menveo® and Menactra® groups, respectively, for induration >50mm).

Solicited systemic AEs were reported by 41% and 40% of the Menveo® and Menactra® groups; the most commonly reported systemic solicited AEs were headache (28% and 27%, respectively), myalgia (17% in both vaccine groups), and malaise (11% in both vaccine groups). Severe headache was reported by 2% and 1%, respectively, while severe myalgia and malaise were reported by 1% in both vaccine groups.

Serious adverse events in the indicated age group:

Serious adverse events (SAEs) occurred in <1% of subjects at any time during the studies in the Menveo® and Menactra® groups (40 of 6185 subjects = 0.6% and 13 of 1757 subjects = 0.7% respectively). SAEs during Month 1 occurred in 7 Menveo® recipients, 4 Menactra® recipients and 1 Tdap recipient. None of the reports of these SAEs raised concerns regarding causality. Neurologic and psychiatric events were reviewed specifically: five Menveo® recipients and one Menactra® recipient experienced one or more events of suicide attempt or intentional drug overdose between 10 and 156 days post vaccination. Three participants experienced seizure and one participant experienced syncope in the Menveo® group and one participant experienced auditory hallucinations in the Menactra® group (occurred between 21 to 151 days post vaccination). These neurologic and psychiatric events varied widely in their presentations and temporal relationship to vaccination, and were not considered by the clinical reviewer to raise concerns regarding causality.

Among the 5209 women enrolled in the studies, 37 pregnancies occurred among 4115 Menveo® recipients (7 spontaneous abortions, no congenital anomalies) and 6 pregnancies occurred among 1013 Menactra® recipients (no spontaneous abortions, one congenital anomaly [hydrocephalus] that resulted in neonatal death). The estimated dates of conception for the seven Menveo® subjects with adverse pregnancy outcomes, were 5 days prior to vaccination (1 subject), 6 to 17 weeks post vaccination (5 subjects), and 6 months post vaccination (1 subject). The Menactra® subject's estimated date of conception was approximately 15 weeks post immunization.

Pharmacovigilance

No safety issue has been identified that would warrant a Risk Evaluation and Mitigation Strategy (REMS) at this time.

*Adverse Event reporting***:** The sponsor must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and must submit distribution reports as described in (21 CFR 600.81). In addition, the sponsor will provide expanded adverse experience reporting (in addition to complying with the requirements under 21 CFR 600.80) to the Vaccine Adverse Reporting System for one year following product licensure as follows:

1. As 15 day reports: All serious adverse events whether expected/labeled or unexpected/unlabeled.

2. As 30 day (monthly) reports if not already submitted as 15 day reports: all allergic events, including anaphylaxis; neurological events including Bell's palsy, Guillain-Barré Syndrome, encephalitis, encephalopathy, brachial neuritis, optic neuritis, other neuropathy, myelitis including transverse myelitis, ptosis, ataxia, multiple sclerosis, acute disseminated encephalomyelitis, cerebrovascular accidents, and transient ischemic attacks; idiopathic thrombocytopenic purpura; Kawasaki disease; myasthenia gravis; other new onset autoimmune disease; and all cases of non-intentional injury.

Current Status of Postmarketing Studies subject to reporting requirements of 21 CFR 601.70:

1. The sponsor will conduct a Phase IV self-controlled case-series study to expand the understanding of the safety profile of Meningococcal [Groups A, C, Y, and W-135] Oligosaccharide Diphtheria CRM197 Conjugate Vaccine in a minimum of 50,000 HMO subjects 11 through 19 years of age. CBER reviewed this draft protocol (V59_34) and provided comments to Novartis on December 23, 2009. Novartis responded with a second draft protocol on January 5, 2010. This revised protocol was acceptable to CBER with the exception of masking procedures for clinical reviewers. In a telecon on January 7, 2010, Novartis agreed to the masking procedures requested by CBER. The final IRB approved study protocol will be submitted no later than June 20, 2010. The study will be initiated by August 20, 2010. The final study report will be submitted by 1 year after the last subject has completed the study and no later than August 20, 2015.

2. The sponsor will collect pregnancy safety data for Meningococcal [Groups A, C, Y, and W-135] Oligosaccharide Diphtheria CRM197 Conjugate Vaccine by means of the Vaccine and Medications in Pregnancy Safety Surveillance [VAMPSS] program. VAMPSS will prospectively enroll individuals exposed to Meningococcal [Groups A, C, Y, and W-135] Oligosaccharide Diphtheria CRM197 Conjugate Vaccine during pregnancy, and odds ratios for several outcomes (spontaneous abortions, preeclampsia, fetal deaths, preterm births, intrauterine growth restriction, total major congenital malformations, and specific major malformations) will be calculated. Individuals identified by VAMPSS without documented exposure to known teratogens and without exposure to Meningococcal [Groups A, C, Y, and W-135] Oligosaccharide Diphtheria CRM197 Conjugate Vaccine will serve as controls. VAMPSS will also identify infants with specific malformations and perform case control analyses to determine the odds of exposure to Meningococcal [Groups A, C, Y, and W-135] Oligosaccharide Diphtheria CRM197 Conjugate Vaccine. CBER has reviewed a synopsis for both arms of the pregnancy surveillance program. The final IRB approved pregnancy registry protocols will be submitted by August 20, 2010. Subject accrual and data collection will begin at the time of CBER's approval of the protocol and end no sooner than five years later. The U.S. pregnancy registry may be considered completed one month after discontinuation of patient accrual for the purpose of preparing a five-year final summary report. The five-year final summary report should be submitted to CBER five years and six months after initiation of patient accrual and data collection. After CBER review of the five-year data, the need to continue further data collection in the U.S. pregnancy registry will be discussed with CBER. CBER will have final approval regarding any decision to discontinue the U.S. pregnancy registry

AGREED UPON POSTMARKETING COMMITMENTS

Written commitments as described in Novartis letter of 15 January 2010 are outlined below:

Postmarketing Studies subject to reporting requirements of 21 CFR 601.70.

1. To conduct a randomized, comparative trial, designed primarily to evaluate the potential for immune interference of concomitant use of Menveo® with U.S. licensed human papillomavirus vaccine and tetanus, reduced diphtheria, acellular pertussis vaccine as currently recommended for immunization of adolescents. You commit to providing a clinical protocol for CBER review by July 2010 and to providing complete study results by November 2012.

2. To conduct a Phase IV self-controlled case-series study to assess the safety of Meningococcal [Groups A, C, Y, and W-135] Oligosaccharide Diphtheria CRM_{197} Conjugate Vaccine being used by a minimum of 50,000 HMO subjects 11 through 19 years of age to expand the understanding of the safety profile of Meningococcal [Groups A, C, Y, and W-135] Oligosaccharide Diphtheria CRM_{197} Conjugate Vaccine. The final IRB approved study protocol will be submitted no later than June 20, 2010. The study will be initiated by August 20, 2010. The final study report will be submitted by 1 year after the last subject has completed the study and no later than August 20, 2015.

3. To establish a U.S. pregnancy registry to collect safety data on spontaneously-reported exposures to Meningococcal [Groups A, C, Y, and W-135] Oligosaccharide Diphtheria CRM_{197} Conjugate Vaccine during pregnancy and lactation. The final IRB approved pregnancy registry protocol will be submitted by August 20, 2010. Patient accrual and data collection will begin at the time of CBER's approval of the protocol and end no sooner than five years later. The U.S. pregnancy registry may be considered completed one month after discontinuation of patient accrual for the purpose of preparing a five-year final summary report. The five-year final summary report should be submitted to CBER five years and six months after initiation of patient accrual and data collection. After CBER review of the five-year data, the need to continue further data collection in the U.S. pregnancy registry will be discussed with CBER. CBER will have final approval regarding any decision to discontinue the U.S. pregnancy registry.

8. Advisory Committee Meeting

It was determined that review of the vaccine by the Vaccines and Related Biological Products Advisory Committee was not required because this product was not considered substantially different from other conjugated meningococcal vaccines licensed for a similar age-group, and there were no significant issues that required input from the VRBPAC.

9. Pediatrics

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We presented to the FDA's Pediatric Review Committee Novartis' request to waive the pediatric study requirement for ages birth to 2 months because the necessary studies in this age group are impossible or highly impracticable and the product does not represent a meaningful therapeutic benefit in this age group. We waived the pediatric study requirement for infants from birth to < 8 weeks of age because the product does not represent a meaningful therapeutic benefit over initiating vaccination at 8 weeks of age, and the product is not likely to be used in a substantial number of pediatric patients from birth to < 8 weeks of age.

We deferred submission of Novartis' pediatric studies for ages 2 months to 10 years for this application because this product is ready for approval for use in adults and adolescents and the pediatric studies for younger age groups have not been completed.

The deferred pediatric studies required under 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported according to 21 CFR 601.70 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below:

4. Deferred pediatric study V59P14 under PREA for safety and immunogenicity of active immunization for the prevention of disease caused by *Neisseria meningitidis* serogroups A, C, W and Y in pediatric patients 2 months of age (infant 4 dose series at 2, 4, 6, and 12 months of age).

   Final Report Submission: March 31, 2011

5. Deferred pediatric study V59P23 under PREA for safety of active immunization for the prevention of disease caused by *Neisseria meningitidis* serogroups A, C, W and Y in pediatric patients 2 months of age (infant 4 dose series at 2, 4, 6, and 12 months of age).

   Final Report Submission: Interim Study Report December 31, 2011; Final Study Report July 31, 2012

6. Deferred pediatric study V59P21 under PREA for safety and immunogenicity of active immunization for the prevention of disease caused by *Neisseria meningitidis* serogroups A, C, W and Y in pediatric patients ages 7 to 12 months of age.

   Final Report Submission: March 31, 2011

7. Deferred pediatric study V59P20 under PREA for safety and immunogenicity of active immunization for the prevention of disease caused by *Neisseria meningitidis* serogroups A, C, W and Y in pediatric patients 2 to 10 years of age.

   Final Report Submission: March 31, 2010

8. Deferred pediatric study V59P33 under for safety and immunogenicity of active immunization for the prevention of disease caused by *Neisseria meningitidis* serogroups A, C, W and Y in pediatric patients 2 months of age (infant 4 dose series at 2, 4, 6, and 12 months of age).

   Final Report Submission: December 31, 2011

10. Other Relevant Regulatory Issues

N/A

11. Labeling

The Advertising and Promotional Labeling Branch (APLB) recommended that the proposed proprietary name Menveo® be found acceptable.

The package insert submitted by the applicant was in the format required by FDA's Final Rule titled "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" published in January 2006.

All issues were acceptably resolved after exchange of information and discussions with the sponsor.

12. Recommendations

The committee recommends approval of the BLA for Menveo.