Summary Basis for Regulatory Action

Date: April 1, 2011

From: Cara R. Fiore, Ph D, Chair of the Review Committee

BLA/ STN#: 125300/7

Applicant Name: Novartis Vaccines and Diagnostics

Date of Submission: March 4, 2010

PDUFA Goal Date: April 3, 2011

Proprietary Name/ Established Name: MENVEO®, Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM_{197} Conjugate Vaccine

Changes Sought Under This BLA Supplement: To include the re-evaluated immunogenicity data due to a transcription error that lead to the revision of V59P13 and V59P18 immunogenicity data in the original submission (125300_0) and to revise the package insert to reflect this change.

Recommended Action: Approval

Signatory Authorities Action: Approval

Offices Signatory Authority: Wellington Sun, M.D., Director, Division of Vaccines and Related Products Applications, Office of Vaccine Research and Review

√ **I concur with the summary review.**

□ **I concur with the summary review and include a separate review to add further analysis.**

□ **I do not concur with the summary review and include a separate review.**

Table 1: Review documents used in compiling this SBRA:

Review Category	Reviewer--date of review
Clinical Review	Margaret Bash, MPH, MD - 01 April 2011
Statistical Review	Barbara Krasnicka, PhD - 22 February 2011
CMC Review	Mustafa Akkoyunlu MD, PhD - 10 November 2010
Bioassay Review	Martha Lee, Ph D - 07 February 2011
Container and Labeling	Catherine Miller, Maryann Gallagher - 16 December 2010

1. Introduction

MENVEO® (also referred to as MenACWY in this document), manufactured by Novartis Vaccines and Diagnostics S.r.L. Bellaria-Rosia, 53018 Sovicille, -b(4)-, Italy (Novartis) is a Meningococcal (Groups A, C, Y and W-135) Oligosaccharide Diphtheria CRM_{197} Conjugate Vaccine for prevention of invasive meningococcal disease caused by *Neisseria meningitidis*, serogroups A, C, W-135, and Y. The vaccine was approved by the FDA for use in individuals 11-55 years of age in the U. S. on February 19, 2010. On March 4, 2010, the sponsor reported a transcription error in the specification of one of three assay controls that were used to assess the day-to-day performance of the hSBA assay. The affected hSBA assays were used to evaluate responses to Menveo in the clinical studies V59P13 and V59P18. The transcription error specifically concerned the range for the MenC-high control (-b(4)---------- serum used in the studies V59P13 and V59P18. The re-evaluated immunogenicity data and the resulting revisions to the package insert were evaluated under this supplement.

On March 31, 2010, Novartis submitted sBLA 125300_95 to expand the indication of MENVEO® vaccine to include use in children 2 through 10 years of age for prevention of invasive meningococcal disease caused by *Neisseria meningitidis*, serogroups A, C, W-135 and Y. This supplement was approved on January 28, 2011.

On December 10, 2010, the firm submitted additional data for the current supplement (125300_7) that resulted in a major amendment, with a new action due date of April 3, 2011.

2. Chemistry Manufacturing and Control (CMC)

MENVEO consists of four drug substances, each composed of a Meningococcal capsular oligosaccharide covalently attached to the nontoxic 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).

Full review of CMC information for MENVEO was completed at the time of original licensure on February 19, 2010. All lots of vaccine used in the clinical study of concomitantly administered

vaccines were reviewed and released for distribution by CBER. The CMC review in this supplement concentrated on the human serum bactericidal assay (hSBA).

Serology Assay Review:
The hSBA (human Serum Bactericidal Assay) is used to measure specific antibody titers (Groups A, C, Y and W-135) in sera from the subjects in clinical trials in order to evaluate the immune response before and after vaccination with the quadrivalent vaccine directed against the serogroups A, C, W-135 and Y of *Neisseria meningitidis.* The antibody mediated hSBA titer following vaccination serves as a marker for the immunogenicity of the vaccine. Briefly, the serum bactericidal assay is based on the measurement of complement dependent killing of bacteria through the binding of serogroup specific antibodies of the meningococcal strains. The C1q subunit of the complement system binds to the Fc portion of the bound antibodies, which activates the classical complement pathway, resulting in lysis of the meningococci. The hSBA titer is defined as the reciprocal value of the interpolated serum dilution that kills 50% of the bacteria used in the test.

The validation of the SBA is presented in the Section 5.3.1.4.1 of the original BLA (125300.0). File name: hSBA Validation-report. Document name: "Serum Bactericidal Assay for the Determination of Complement Fixing Antibodies against *Neisseria Meningitidis* Serogroups A, C, W-135, Y." The SOP of the SBA is "SOP NO. 222582" and it is located in 125300.015 (5.3.1.4.1). The SOP was still valid and it was cited in support of this file.

CMC Recommendations:

The SOP and the validation protocol of the hSBA were evaluated during the original application of Menveo and found to be satisfactory for the measurement of serum bactericidal activity. The sponsor has not made any changes to the hSBA test method since the original approval of Menveo. As per the SOP each assay plate contains three quality controls sera that are treated exactly the same way as the test samples. In order to validate the assay, each control has to pass its predefined specification. Should one control be out of specification, the assay is invalid and has to be repeated. Thus, the sponsor's action to eliminate the samples that were present in the invalidated assay plates is appropriate.

CBER Lot Release
There are no ongoing or pending investigations or compliance actions with respect to the above facilities or their product(s). Therefore, the Office of Compliance and Biologics Quality, Division of Case Management does not object to the approval of this supplement.

3. Clinical

Following approval of the Biologics License Application (BLA) for Menveo on February 19, 2010, Novartis submitted to the file an efficacy information supplement classified as "Changes Being Effected (CBE)" as a mechanism to inform the Agency about an error that affected some of the serology data submitted to support the original licensure. The supplement described a transcription

error for the acceptable range for the high control serum used in the serogroup C hSBA assay. The error was discovered during an evaluation of the historical performance of assay controls and affected the validity of a subset of serogroup C immunogenicity results from clinical studies V59P13 (pivotal immunogenicity, lot consistency study) and V59P18 (concomitant immunization study) submitted to the original BLA.

Based on the transcription error, the acceptable range for the high titer control was considered to be ---b(4)----------. Therefore, some assays in which the high control titer obtained was lower than the true accepted lower limit were considered valid, and the assays were not repeated as they would have been per Standard Operating Procedure (SOP) if the correct acceptable range for the high control was used. Novartis indicated that this error affected 349/6735 sera results (5.2%) in V59P13 and 60/3085 sera results (1.9%) in V59P18. Uncorrected data from these studies had been included in the approved package insert.

Novartis assumed that the affected samples were a random selection of the full set of available samples and considered the results of the analyses (see tables copied below) to show that the conclusions presented in the clinical study report (CSR) and regulatory package insert/monographs were unaffected. Thus, taking into consideration these analyses and in accordance with the company SOPs, Novartis indicated they would not re-open the database for either study. According to Novartis, any subsequent use of data derived from these studies would be based on the uncorrected dataset submitted with the original license application.

Following the initial review of this supplement, Novartis was asked to evaluate the distribution of affected titers with respect to demographic variables. The affected titers appeared to be randomly distributed within and among the vaccine groups. Additional affected titers were identified as those from assays that were repeated when the original assay was erroneously considered invalid. For these affected titers, the first valid titer should have been used. Novartis was asked to re-evaluate the worst case scenario for possible effects of the transcription error on overall outcomes of the study. The worst case scenarios conducted in which all affected MENVEO titers were considered non-responders, and all Menactra were considered responders still met non-inferiority criteria. The worst case scenario in which titers were considered 4x or $1/4^{th}$ the reported titer (range of assay variability) also did not affect conclusions based on analyses of the primary endpoints of the pivotal study V59P13.

Corrected datasets were received, and although the overall conclusions of the pivotal study were not affected, CBER determined that the data in the package insert should be corrected.

Clinical Recommendations:

Approval with incorporation of corrected data into the package insert. The Clinical Study Reports should be amended to reflect the corrected data.

4. Statistical

The objective of this BLA supplement submission was to show that the discovered transcription error did not influence conclusions that were presented in the clinical study report (CSR) and regulatory package insert.

According to the applicant's finding, 5% (335/6706) MenC-hSBA results from V59P13 and 1.9% (60/3079) of MenC-hSBA results from V59P18 results were falsely validated and released for further analysis based on the false specification of the high control range. Therefore, to evaluate the possible influence of the transcription error, immunogenicity datasets for pivotal studies were redefined, the statistical analyses were rerun, and influence of the additional missing immunogenicity data was assessed.
In the case of clinical trial V59P13, for all three primary immunogenicity objectives (lot-to-lot-consistency, two non-inferiority hypotheses for two age groups), it appears that the transcription error had a negligible influence on the conclusions derived for the primary hypotheses for serogroup C. However, due to the missing data and the deviation from the original randomization and random selection of serum samples, biases could be introduced to the studies' results.

Insignificant numerical differences were noticed across the statistical analyses, which were performed to assess the impact of the transcription error on the results of testing primary hypotheses. Therefore, the interpretations of the results and conclusions derived from the trials and stated in the clinical study report (CSR) and regulatory package insert remained unchanged. However, the estimations of endpoints and their confidence intervals should be revised in the CSR and the regulatory package insert.

In the case of clinical trial V59P18, despite the fact that the transcription error did not have impact on the conclusions for the serogroup C, the trial primary hypothesis #3 was not met. For the serogroup W, the lower limit of the two-sided 95% CI for the difference in the percentages of seroresponse rates to MenACWY administered after Tdap and MenACWY alone was lower than the -10% non-inferiority margin, the lower limit of CI was -20.29%. This means, the pre-specified study success criterion was not met because one co-primary null hypothesis was not rejected.

Due to missing data and the fact that different serum assay runs were used for different study groups (sera from Groups II and III were not assigned at random to assay runs), additional biases could be introduced into the results.

Recommendation: As the statistical evaluations demonstrated small influence of the transcription error on the statistical results, it appears that the interpretations of the results and conclusions stated in the clinical study report (CSR) and regulatory package insert can remain unchanged. However, the estimations of endpoints and their confidence intervals should be revised in the CSR and regulatory package insert.

5. Bioassay Statistical

Study V59P13: After examination of the various sensitivity analyses, the conclusions as presented in the clinical study report (CSR) and regulatory package insert/monographs remain unaffected. Only small numerical differences were introduced across all of the sensitivity analyses with the interpretation of the findings unchanged.

Study V59P18: Similar to the analysis performed with the pivotal V59P13 study, even with the more aggressive negative assumptions for the results of revised testing results, the conclusions as communicated in the CSR are unchanged.

6. Labeling

The package insert (PI) was evaluated by the entire review committee of the supplement. Each committee member contributed to internal discussions. After several minor revisions to the PI by the applicant, the committee determined that the prescribing information is acceptable. These changes to the tables in the PI have been incorporated into PI along with the changes for BLS 125300_49. That PI contains updated changes from 125300_7 and 125300_49.

7. Postmarketing

There are no post marketing studies necessary for this supplement.

8. Pediatrics

This supplement did not trigger a pediatric assessment as per provisions in the Pediatric Research Equity Act because the application was not submitted to support new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration.

9. Advisory Committee Meeting

There were no significant issues related to this sBLA that required input from the Vaccines and Related Biologics Products Advisory Committee.

10. Recommendation

The committee recommends approval of the BLA supplement. The sponsor was requested, in the Approval Letter, to update the data in the Final Clinical Study reports by submitting addenda to STN 125300_223 as product correspondence.