Summary Basis for Regulatory Action

Date: April 1, 2011

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

BLA/ STN#: 125300/49

Applicant Name: Novartis Vaccines and Diagnostics

Date of Submission: March 18, 2010

PDUFA Goal Date: April 17, 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 data regarding persistence of meningococcal antibodies in adolescents through 21 months following first vaccination with MENVEO 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.**

Review Category	Reviewer--date of review
Clinical Review	Margaret Bash, MPH, MD 01 April 2011
Statistical Review	Barbara Krasnicka, Ph.D. 22 March 2011
CMC Review	Mustafa Akkoyunlu MD, Ph.D. 10 November 2010
Bioassay Review	Martha Lee, Ph D 07 February 2011
Container and Labeling	Catherine Miller - June 4, 2010

Table 1: Review documents used in compiling this SBRA:

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. MENVEO was approved by the FDA for use in individuals 11 through 55 years of age in the U. S. on February 19, 2010 based primarily on safety and immunogenicity data from pivotal clinical trial V59P13.

Supplement BLA 125300_49 is providing data:

1. To support demonstration that MENVEO vaccine induces a durable immune response, measured through 21 months after vaccination.
2. To compare persistence of hSBA titers induced by MENVEO® and Menactra vaccines.

The assessment of meningococcal antibody persistence in adolescents through 21 months following the first vaccination with MENVEO was based on clinical study V59P13E1 that was an extension of pivotal trial V59P13. Subjects enrolled in trial V59P13, who were 11-18 years of age at study enrollment with hSBA results available for at least one serogroup at one month after vaccination, were asked to enroll in this extension study. More specifically, the extension study aims to assess the persistence of immune responses at 21 months, 3 years, 5 years, and 7 years following vaccination.

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. sBLA 125300_95 was approved on January 28, 2011.

On December 20, 2010, the firm submitted additional data for this supplement (125300_49) that resulted in a major amendment, with a new action due date of April 17, 2011.

2. Chemistry Manufacturing and Controls (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 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 measures 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 Standard Operating Procedure (SOP) of the SBA is "SOP NO. 222582" is located in 125300.015 (5.3.1.4.1).

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 licensure of MENVEO. Therefore, the hSBA results presented in this BLA are based on a validated hSBA. However, since the validation document indicates that the assay needs to be validated at least every –b(4)- from the previous validation, the sponsor needs to perform a new validation study before submitting hSBA results in support of future BLAs. This was communicated to the applicant on April 09, 2010.

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

Background

BLA 125300/49 provides an evaluation of the persistence of bactericidal antibodies in adolescents at 21 months post-immunization with the quadrivalent meningococcal conjugate vaccine, MENVEO. The purpose of this supplement is to modify the package insert to include a description of antibody persistence.

During the period from 1998 to 2008, invasive meningococcal disease occurred in the U.S at an estimated incidence rate of 0.5 to 1.1/100,000 (1). 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 support licensure of MENVEO in the U.S. was to compare safety outcomes and serum bactericidal antibody responses following vaccination with MENVEO or the U.S.-licensed vaccine Menactra®.(Meningococcal Groups (A, C, Y, and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine.)

The bactericidal activity of serum from vaccine recipients is considered 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. Sero-epidemiologic studies by Goldschneider et. al., showed protection from disease in individuals whose sera killed the circulating strain when diluted 1:4 (2). Menactra was licensed in 2005 on the basis of immunologic (SBA) non-inferiority to Menomune®, a meningococcal polysaccharide vaccine licensed in 1981 in the U.S. MENVEO was licensed in 2010 on the basis of immunologic non-inferiority to Menactra. In this application, bactericidal assays using an extrinsic source of human complement (hSBA) were used.

Study Design (V59P13E1)

The study design is open-label, with recruitment of a subset of both MENVEO and Menactra recipients from the per-protocol adolescent cohorts of the pivotal safety and immunogenicity study V59P13 (BLA 125300/0). In addition, a separately enrolled age-matched unimmunized group was included. The study is intended to determine the persistence of bactericidal antibody responses to MENVEO at 21 months, 3 years, 5 years and 7 years post one dose of vaccine. The interim results for the 21 month time-point are submitted in this supplement to support a labeling change regarding persistence of antibody responses. The immunogenicity analyses are primarily descriptive.

This submission consists of the data for the 21 month follow-up time point. In addition, the study is designed to collect information about new medical diagnoses among the study participants followed long-term.

Safety

Data regarding new medical diagnoses between completion of V59P13 and V59P13E1 were submitted. The small study size, and open-label enrollment, and exclusion criteria for enrollment that

includes chronic medical conditions, limit the usefulness of the study for evaluating long-term safety. Review of the data revealed no patterns of new diagnoses that raised concerns for causality.

Immunogenicity

Pivotal immunogenicity data to support lot consistency and non-inferiority to Menactra were provided in study V59P13 under BLA125300/0. Immunogenicity persistence was evaluated on subsets of the per protocol population for each serogroup and for a separately enrolled age matched naïve group (Table 1).

Table 1: Persistence of immune responses through 21 months post vaccination among adolescents vaccinated with one dose of MENVEO or Menactra

	% hSBA ≥1:8 (95% CI)			**hSBA GMTs (95% CI)**		
Serogroup	**MENVEO**	**Menactra**	**Naive**	**MENVEO**	**Menactra**	**Naive**
A	N=275	N=179	N=97	N=275	N=179	N=97
	36 (30, 42)	23 (17, 30)	5 (2, 12)	5.29 (4.63, 6.05)	3.5 (2.97, 4.14)	2.36 (1,88, 2.96)
C	N=275	N=179	N=97	N=275	N=179	N=97
	62 (56, 68)	59 (52, 66)	42 (32, 53)	10 (9.02, 12)	8.96 (7.51, 11)	5.95 (4.68, 7.56)
W-135	N=273	N=176	N=97	N=273	N=176	N=97
	84 (79, 88)	74 (67, 80)	51 (40, 61)	18 (15, 20)	14 (12, 17)	7.80 (6.11, 9.97)
Y	N=275	N=179	N=97	N=275	N=179	N=97
	67 (61, 72)	54 (47, 62)	40 (30, 51)	12 (10, 14)	7.85 (6.54, 9.43)	5.14 (4.01, 6.60)

The clinical review focused on evaluating the representativeness of the enrolled populations in comparison to the original study population. Demographic characteristics of the subsets enrolled in V59P13E1 were similar to the original study population, accounting for the time interval in age. Comparison of pre- and 1 month post-immunization hSBA titers for the per-protocol groups of V59P13, and the subsets studied for persistence in V59P13E1 did not reveal substantial differences. The review of study V59P13E1 did not reveal evidence of obvious selection bias, but it should be noted that the study design is subject to unrecognized bias.

Prior to submitting this supplement, Novartis notified CBER that a transcription error for the normal range of one control serum used in the group C hSBA assay resulted in reporting of some invalid results in the original study V59P13. During the review of this supplement, Novartis was asked to revise the data sets for V59P13 (BLA125300/07), and to revise the data sets for V59P13E1 for those

individuals who were no longer eligible because of an invalid group C hSBA result at the pre- or 1 month post immunization time point in V59P13. The data sets, and the proposed data to be included in the package insert, have been corrected.

During clinical development, CBER conveyed to Novartis that an immune response that is determined to be statistically significantly higher than another immune response would not be interpreted or used as evidence of superior protection from meningococcal disease. Explicit or implicit superiority claims based on the immunogenicity data reviewed are not appropriate for labeling purposes. The proposed label does not include a statistical comparison between MENVEO and Menactra or unimmunized controls (Table 1).

The final draft label was reviewed and is acceptable.

Recommendations: Approval

Although there are study design limitations described in this clinical review, the relatively poor persistence of bactericidal antibody titers at less than 2 years following a single dose of MENVEO is considered clinically important information. Approval of changes to the package insert to include the proportion with hSBA titers ≥1:8 and geometric mean titers is recommended. Inclusion in labeling of antibody persistence data for the comparator group, Menactra, and the separately enrolled age-matched unimmunized group is recommended. This information provides an understanding of background seropositivity, vaccine effect, and the decline in vaccine effect over time for both MENVEO and the comparator vaccine from a study in which all sera were assayed in the same laboratory using a validated hSBA assay.

1. A.C. Cohn, J.R. MacNeil, L.H. Harrison, C. Hatcher, J. Theodore, M. Schmidt, *et al.*, Changes in *Neisseria meningitidis* disease epidemiology in the United States, 1998-2007: implications for prevention of meningococcal disease, *Clin Infect Dis* **50** (2) (2010), pp. 184-91.

2. Goldschneider I, Gotschlich EC, Artenstein MS. Human immunity to the meningococcus. I: The role of humoral antibodies. J Exp Med 1969;129:1307--26.

4. Statistical

Objective of the STN 125300_49 BLA submission (March 18th, 2010) was to support changes to be introduced to the approved package insert (PI) for MENVEO. The changes are pertinent to the persistence of meningococcal antibodies in adolescents through 21 months following the vaccination with MENVEO®. An assessment of meningococcal antibodies persistence in adolescents through 21 months following the first vaccination with MENVEO® was based on clinical study V59P13E1 that was an extension of pivotal trial V59P13. Subjects, who participated in trial V59P13, 11-18 years of age at study enrollment, and for whom hSBA results for at least one serogroup at one month after vaccination were available, were asked to be enrolled in this extension study. Immunogenicity data, at 21 months after vaccination and for each serogroup, indicated that the GMTs in subjects vaccinated with MENVEO® or Menactra® were higher than for the Naïve subjects, and GMTs for the

MENVEO® group were higher than for the Menctra® group. The same trend was observed for the estimations of percentages of subjects with hSBA $\geq$ 1:8 at 21 months after vaccination.

Recommendations

The descriptive analysis of immunogenicity data supports the applicant's proposed changes to the package insert for MENVEO®. However, the applicant should revise tables in the Clinical Study Report; due to the transcription error, 9 subjects should be removed from the population of study V59E13E1.

5. Bioassay Review

Trial V59P13E1 was a Phase 3b, multi-center, open-label, controlled study. Sites participating in V59E13 trial that had adequate (higher) enrollment were selected. Subjects who participated in V59P13 trial (11-18 years of age at V59P13 study enrollment), with available human serum bactericidal assay (hSBA) result from at least one serogroup at one month after vaccination, were asked to be enrolled in this extension study.

Based on the submitted data, 2364 of 2388 (99%) lab analyses were conducted in May 2009 and 24 (1%) in June 2009. Therefore, the assay validation in 2005 stands and there are no assay re-validation concerns for this submission.

A laboratory SAS data file for V59P13, which incorporates the effects due to transcription error issues detailed in BLA 125300/7 supplement, has been re-submitted by the applicant and verified by the bioassay reviewer.

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.

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. Novartis 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.