# Complete Response Letter - Menveo

**STN: BL 125300/0**

Novartis Vaccines and Diagnostics, Inc.
Attention: Chris Webster, Ph.D.
350 Massachusetts Ave.
Cambridge, MA

Dear Dr. Webster:

We have completed the review of your August 28, 2008 biologics license application (BLA) for Meningococcal Polysaccharide (Serogroups A, C, Y, W-135) CRM197 Conjugate Vaccine submitted under section 351 of the Public Health Service Act.

We acknowledge receipt of your amendments dated November 21, 2008, December 5, 2008, December 19, 2008, January 15, 2009, February 6, 2009, March 9, 2009, March 30, 2009, April 10, 2009, April 17, 2009, May 6, 2009 and May 15, 2009, June 17, 2009, and June 22, 2009. We further acknowledge receipt of your amendment dated February 24, 2009, and note that this amendment contains a clinical study report that was submitted in response to our request for additional information regarding pertussis vaccine serology; however, as agreed upon during the telecon dated April 9, 2009, the data that address the concomitant administration of Gardasil will be resubmitted separately as a supplement to support a label change. You may cross reference applicable sections of any of these amendments in your complete response to this letter and we will review those sections as a part of your complete response.

Our review finds that the information and data submitted are inadequate for final approval action at this time based on the deficiencies outlined below. Please note that to simplify our comments below, we will refer to your product by the proposed proprietary name, Menveo.

The deficiencies are as follows:

**CMC:**

1. The following sections of the manufacturing process have not been completely validated:

a. As mentioned in our telecon of March 23, 2009, the revalidation data of the ----------b(4)---------- of MenA, C, Y, and W-35 strains must be submitted prior to approval.

b. Please establish and provide data to support mixing times for all critical steps in the manufacture of Menveo.

c. Please establish and provide data to support time limits for all critical manufacturing steps for Menveo.

2. The acceptance criteria for data which are written in Table 2.3.S.2.5-3. are presented as number of --b(4)-------- in amount. The -----b(4)----------are much more relevant than the --b(4)------- because, ultimately, it is the --b(4)---------- that are important when injected into humans. Please submit these data and specifications in -----b(4)----------

3. You have submitted 9 month and 18 month stability data at 2-8° C for process validation and subsequently manufactured lots of Drug Product. This data

does not include a complete battery of test at all time points. In your stability protocol the test for sterility is performed at zero time and not again until the 24 month time point. Please submit stability data for sterility taken at a time point greater than 12 months, along with the complete battery of tests, including all proposed test for process validation lots of Drug Product.

4. You have proposed --b(4)---------- from manufacture after licensure because you feel that consistency has been demonstrated. This is not sufficient justification for --b(4)----------. For example, in the MenY-CRM Conjugate, Justification of Specification (3.2.S.4.5), page 12, the ----------b(4)---------- ---------. We therefore encourage the -----b(4)---------- ---------- to insure manufacturing consistency. As is illustrated in the above example the impact --b(4)---------- on product manufacturing may be negative and must be considered. Please submit a detailed justification that includes impact assessment of ---b(4)---------- being considered for --b(4)---------- in the manufacture of Menveo and for lots submitted for purposes of licensure.
5. The following lot release and stability specifications are not adequately justified. Please comment on the rationale for the following testing specifications:
   a. Specifications for --b(4)----------: The specifications for ------b(4)--------- are not consistent among the four conjugates; i.e. the MenA conjugate has different specifications than MenC, MenW and MenY, despite having similar precision for -------b(4)--------- results for all four serogroups. Specifications for MenA conjugate have been set at -b(4)- of the target concentration of -b(4)- of -b(4)------, whereas specifications for MenC, MenW and MenY conjugates have been set at -b(4)- of target concentration of --b(4)---. Based on the data from lot release testing and stability and the precision of test for --b(4)----------, a specification of greater than --b(4)- of target concentration for all serogroups is not justified. Please consider revising the specification for --b(4)---------- for menC, menW, and menY to not greater than-b(4)-or provide a justification for the current specification of -b(4)-
   b. Specifications for --b(4)----------, which is a critical parameter to ensure potency of vaccine during its shelf life is set at -b(4)-. We do not consider this specification justified based on lot release testing and stability data submitted. These data do not justify setting specifications at more than --b(4)----------. Please consider revising the specification for --b(4)---------- to not greater than -b(4)- or a value that is more consistent with the data submitted in the BLA.
   c. The specifications for protein concentration --b(4)---------- of Drug Product, Menveo, MenA Lyophilized has a wide range, and Menveo, MenCWY Liquid does not have any specifications for total protein. Please set total protein specifications for Menveo, MenCWY Liquid and please

consider setting the total protein specifications with a more narrow range for Menveo, MenA Lyophilized.

d. Specifications for endotoxin of the Drug Product --b(4)---------- for MenA Lyophilized Conjugate and --b(4)----- for MenCWY Liquid) are not supported by the data submitted. These specifications should be based on data and manufacturing process capability. Please either submit the data on which the endotoxin specifications are based, or revise and justify the specifications based on the data in the BLA.

e. Purity specification for CRM197 has been described as -b(4)-. Data reported from all lots have purity reported as not less than -b(4)- Please justify a specification of -b(4)- or consider setting purity specification, based on data in the BLA, at -b(4)--

6. Several process and release methods have not been properly validated. Please address the following comments on the Method Validations:

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

b. Accuracy Studies were not properly evaluated as illustrated in the examples below. Further, accuracy studies should be evaluated by calculating recovery of the spiked quantity of materials, not from total of starting sample plus spiked material. Please re-calculate spike recovery for all methods for Drug Substances and Drug Products.

i. For the --b(4)----- assay for MenA-CRM, validation report -b(4)- 07.122 VR 7, please justify the use of the -b(4)- standard as a spiked material to demonstrate accuracy of the -b(4)--- method. Accuracy should be evaluated using a spiking material identical to or as similar to the analyte as practicable. Evaluation of accuracy should be performed using CRM or preferably CRM:MenA as a spiking material.

Table 5.c. “Accuracy in CRM-Men 13.220 Lot -b(4)----” indicates a protein concentration of the unspiked lot of -b(4)----. Subsequently a spiked amount of --b(4)---------- is determined as a protein concentration of -b(4)----- and recovery evaluated as -b(4)-. Please verify the data and calculations presented and provide a revised table, if necessary.

ii. With respect to the method for the --b(4)-------- assay for polysaccharides of MenA, MenC, Men Y and Men W, accuracy studies have been performed by spiking with ----b(4)----------. Accuracy should be evaluated using a spiking material identical or as similar to the analyte as practicable. In this case, samples from ---b(4)---------- be used for spiking. Alternatively, accuracy of this method could be demonstrated by comparing this method to a reference or another approved method. Please comment.

iii. -b(4)---, MenA-Lyophilized, -b(4)- 07.155 VR.2 Rev. 0 In the evaluation of accuracy, please report actual unspiked and spiked sample results in -b(4)-------- in addition to % recovery results.

c. Several submitted analytical validation studies evaluate procedural range based on linearity of the standard curve. As recommended in ICH Q2(R1), "Validation of Analytical Procedures", the range of a procedure is established by confirming that the analytical procedure provides an acceptable degree of linearity, accuracy and precision when applied to samples containing amounts of analyte within or at the extremes of the specified range of the analytical procedure. Please confirm that the procedural range for all methods used for release testing of Drug Products and Drug Substances, are as described in the ICH Q2 (R1). During our review we have found examples that may not meet the recommendation in ICH Q2(R1). For example:

i. Regarding the --b(4)---------- assay procedures for -b(4)-, MenC, MenW, MenY, and MenA CRM, Report #226491 (VR 5 Rev.0, VR 6 Rev.0, VR 7 Rev.0, and VR 8 Rev.0), please submit an evaluation of the range of this assay. Evaluation of range should be based on precision and accuracy data from actual samples or fortified representative matrix.

d. You have demonstrated linearity of analytical methods from the standard curve. Linearity across the range of method should be demonstrated using samples for which the method is to be used. This has been observed for all the method validations submitted with this application. Please perform additional studies to demonstrate linearity across the range of the method with appropriate samples for all methods used for release testing of Drug Products and Drug Substances.

e. We have the following questions regarding the validation of the -b(4)-- method used as an identity test as is cited in the following documents:

- 
  - ----b(4)----------
  - ----b(4)----------
  - ----b(4)----------
  - ----b(4)----------
  - -b(4)-07.166 VR4 Rev.0 (for identity test of CRM-MenC, in filled Product --b(4)-- (5 mcg/dose) and in product --b(4)------.

i. Validity criteria for the analysis/evaluation of results, as per SOPs (SOP 201717-03 [-b(4) 07.209] and SOP 201711-02 [b(4) 07.166]), state that the --b(4)---------- must not be --b(4)----------. This --b(4)-------- value is not supported by the data submitted. Please reevaluate this parameter for the identity test.

ii. The limits for positive and negative controls are not sufficiently different to provide a clear distinction between these positive and negative controls. SOPs (SOP 201717-03 [-b(4)- 07.209] --b(4)---------- of -b(4)---------- with CRM: -b(4)---------- method (applies to CRM-MenA, -MenW and -MenY) and

SOP 201711-02 [b(4) 07.166] --b(4)---------- CRM-Men C- ---b(4)-------- method), validity criteria for analysis of positive and negative controls (Section 4.5 of SOP 201717-03 and section 4.7 of SOP 201711-02) state:

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

These criteria could result in a small difference between positive and negative samples or controls in a valid assay. Please re-evaluate validity criteria for positive and negative controls so that there is a more distinct (i.e., greater) difference in responses for these controls.

iii. The specificity of ---b(4)----------. You have provided a qualification report for the ----b(4)----------; however, such qualification reports for other --b(4)---------- could not be located in the submission. Please provide the qualification reports for meningococcal groups C, Y, and W-135. Please also provide data to confirm that the ----------b(4)----------

iv. Please confirm the specificity for the identity test for a particular serogroup by using ----b(4)----------. For example, for the identity test of DP, MenCWY, the ---b(4)---------- Please provide evidence that you have checked the ----b(4)---------- in the presence of ----------b(4)----------.

v. Validation report # b(4) 07.166 VR3 R0 for one of the --b(4)-- assays (page 26 of 110 in report) has the ----b(4)----------. As per the validation criteria for this test, specified in the SOP, this test should be deemed invalid. Please clarify if this test was used to generate results.

vi. Validation report # b(4) 07.166 VR3 R0 shows two tests with large differences in -b(4)----- values for ----------b(4)----------. Are these differences typical for this assay? Please comment.

vii. In validation report # b(4) 07.166 VR3 R0, Section 4.2, the Acceptance Criteria for Limit of Detection is defined as ----b(4)---------- Please define in a quantitative manner what is meant in this context by the term “--b(4)----------.”

7. Please provide the additional information regarding the intended use or adequacy of the following analytical procedures and methods:

a. --b(4)---------- SOP 202606 and 202628 -The ----b(4)---------- procedure (SOP 202606) is performed with the ---------b(4)---------- ----- however, the test for --b(4)---------- is performed

following a different procedure (SOP 202628). Please indicate why two different test procedures are used.

b. Regarding the procedures entitled Quantitative Determination of ---b(4)----------, SOP 202152-07 (b(4) 07.023) -This procedure utilizes a ---b(4)---------- while the procedure for ---b(4)----------. Please provide a rationale for the use of a ---b(4)---------- in the procedure for ---b(4)----------

c. There is inconsistency in the methods used for estimating -b(4)--------- in the following procedures. Quantitative determination of --b(4)---------- in CRM-MenA --b(4)----------, SOP 202152-07 (b(4) 07.023), Quantitative determination of -b(4)----- in CRM-MenC, SOP 202157-06 (b(4) 07.030), and Quantitative determination of --b(4)---------- in samples of CRM-MenW and CRM-MenY filled product, SOP 202156-05 (b(4) 07.029).

It is noted that the procedures for --b(4)------- in the CRM-MenY and CRM-MenW glycoconjugates and filled samples utilize an --b(4)---------- to --b(4)---------- for analysis, while the procedures for --b(4)---------- in the CRM-MenA and CRM-MenC glycoconjugates and filled products --b(4)----------. Please justify the use of different techniques --b(4)---------- in these similar assay procedures.

d. For CRM197, Drug Substance, (Section 2.3.S.4 Control of Drug Substance, CRM197----------b(4)---------- with different specifications have been provided. Please clarify how and when each of these two methods are used.

e. The following issues need to be addressed relating to the ---b(4)---------- on monovalent Glycoconjugates, MenC, MenW, MenY and MenA, SOP No. 202781 (English translation 250043):

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

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

8. Organization of Application and Errors

a. Sections on “Validation of Analytical Procedures” were not organized in a manner to provide clear interpretation from the documents submitted. Documents from multiple serogroups of *N. meningitidis* were submitted under “method validation section” for one serogroup. These documents do not provide the purpose and scope of the studies performed, making it impossible for the reviewer to interpret the scope of the studies performed beyond the serogroup for which these studies were primarily performed. In addition, multiple revisions of validation protocols and reports have

been submitted without any details on the changes in multiple revisions. For example, for the Test for --b(4)---------- 14 documents have been provided for MenA Polysaccharide and 8 documents each for MenW and MenY polysaccharides.
In the summary document for each analytical method, for example, Section 3.2.S.4.3.1.5 “Analytical Validation: --b(4)----------,” the purpose and scope of each study for the particular serogroup for which these documents are submitted should be explained clearly. Please provide all method validation reports with details on purpose and scope of various documents, as well as any revisions. If multiple revisions of a document are submitted, details about changes in the revision and purpose and scope of earlier versions should be provided.

b. There are translational and/or typographical errors that make it difficult to make complete and accurate interpretations from the documents and also slow the review process significantly. A few examples of such errors are given below. Please perform a quality check of the entire submission to correct all errors or omissions.

- In SOP 201700-03, page 5, line 8, "--b(4)---------- of [missing word]", “missing word” is not clear.

- In SOP 201707-02 (b(4) 07.139), ----b(4)----------: page 10, “----------b(4)---------- [missing text]”....This statement is incomplete/unclear and difficult to interpret without missing text.
- Regarding the Section 3.2.P.5.2,1.2 Identity MenW-CRM and MenY-CRM of Document 3.2.P.5.2 “Analytical Procedures Menveo, MenCWY Liquid” pages 5 and 6: On page 6, which is stated that the described procedure for Identity of MenW-CRM and MenY-CRM requires the use of --b(4)---------- to establish identity of MenW-CRM and MenY-CRM conjugates. Please comment why --b(4)---------- is used to establish identity of MenW-CRM and MenY-CRMconjugates.

- Please clarify why Document 2.3.S.4 Control of Drug Substance, MenC Polysaccharide, page 4, Section 2.3.S.4 mentions MenA Polysaccharide, when this document and this section are for MenC Polysaccharide.
- Please clarify why b(4) of polysaccharide MenA, MenC, MenW and MenY – -b(4)---- 202138 VP.4 Rev. 0, contains the Validation Protocol for -b(4)-determination of MenC when limit value is for MenW on page 1.

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

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

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

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

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

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

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

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

CLINICAL/statistical comments:

10. Please submit to this license application the protocol for the acceptance criteria and qualification of the human complement used in the hBSA (originally submitted to BB-IND -b(4)-).
11. In the 'Information Amendment First Response Day 75 Letter,' page 31, you stated, "*the assay controls must fulfill preset specifications.*" Please supply specific definitions of these 'preset specifications.'
12. In the 'Information Amendment First Response Day 75 Letter,' page 31, you stated: "*If possible, subjects are tested in numerical order according to subject ID and all visits of a subject are tested in the same assay. This allows for random distribution of both vaccine groups within an assay.*" Please note that ID numbers depended on the baseline randomization and center. Please explain how the above stated procedure of subject serum allocation "allows for random distribution within an assay."
13. Please resubmit the LABDATA file for study V59P13 with the additional information included as follows:. Please also include the ID of the technician who performed the

assay and the non-interpolated titers data (at baseline and Day 29 after vaccination).

14. The seroresponse rates for initially seronegative subjects were greater than for seropositive subjects. However, the definition of seroresponse differs for those who were seronegative pre-immunization vs. those who were seropositive. For each immunogenicity study, please provide an analysis of 4-fold rise using the lower limit of detection titer of 1:4 (rather than half the LOD) for those with baseline titers <1:4 (i.e., post immunization titers of 1:16 or greater) and compare to the rate of 4-fold rise for initially seropositive individuals.
15. There appears to be inconsistency in the determination of severity and relatedness for treatment emergent adverse events, both within and across studies. For example a) in Study V59P17 [table 14.3.1.1.12 Spontaneous abortion] two abortions are listed as severe, while two are listed as moderate; b) in Table 14.3.1.1.16.[(page 9/12) p351 spontaneous and threatened abortion] some events are designated as unrelated while possibly related would be appropriate unless the subjects were not vaccinated, or the abortion was elective; c) severe arthralgia occurring within 30 days of vaccination is designated possibly related in some cases and unrelated in other cases. Inconsistency in the assessment of adverse event severity affects the ability to accurately evaluate and describe the safety profile for this vaccine. Regarding the accuracy of adverse event severity and relatedness, please:

    a.
        a. describe the medical monitoring and quality control of adverse event reporting by study personnel including medical monitors and data safety monitoring committees.
        b. assess the accuracy and consistency of adverse event severity and relatedness reported for each study and all studies combined.
16. Across all studies, the safety follow-up from day 30 to day 180 includes all medically significant adverse events defined as AEs requiring a physician visit, Emergency Department visit, or leading to subject's withdrawal *with the exclusion of* pre-planned visits, medical office visits, or Emergency Room visits for routine medical care and common acute conditions such as: upper respiratory tract infections, otitis media, pharyngitis, urinary tract infections, gastroenteritis, superficial skin infections, and contact dermatitis. Please note that this approach may result in under-reporting due to the subjective categorization of routine or common acute conditions, and could result in lower reporting rates for some events. Please comment.

**Regarding study V59P13 entitled A Phase 3, Randomized, Observer-blind, Controlled, Multi-Center Study to Evaluate the Lot to Lot Consistency of Novartis Meningococcal ACWY Conjugate Vaccine when One Dose is Administered to Healthy Adolescents**
**11-18 Years of Age and to Compare the Safety and Immunogenicity of Novartis Meningococcal ACWY Conjugate Vaccine with that of Licensed Meningococcal**

**ACWY Conjugate Vaccine (Menactra™) when One Dose is Administered to Healthy Subjects 11-55 Years of Age**

17. The plan for serologic subsets is provided in Table 3.1.1.2. The plan as described could have resulted in unblinding of some sera in the serologic assays. In the 11 to 18 year old group, the subset scheme planned for MenACWY differed from the subsets planned for Menactra. The plan called for 1050 MenACWY (350 x three lots) and 300 Menactra sera to be tested for all 4 serogroups, 450 MenACWY (150 x 3 lots) and 150 Menactra to be tested for serogroup C only, and 50 Menactra sera to be tested for groups A and C. Based on the subset plan, no MenACWY samples would be tested for serogroups A and C in the 11 to 18 year old age group. Therefore, approximately 50 sera could have been unblinded. In the planned subset testing for the 19 to 55 year old subjects, 500 MenACWY and 300 Menactra recipients were to be tested for all 4 serogroups, 500 MenACWY and 33 Menactra recipients were to be tested for groups A and C. Based on this plan, the majority of sera from the 19 to 55 year old age group that were to be tested for serogroups A and C were from MenACWY recipients. Please provide the following information and analyses:

    a. Clarify if the participant age group was known for sera.
    b. Provide an analysis of the immunogenicity data for each serogroup by vaccine and by allocation group (i.e., sera selected for all four serogroups, sera selected for A and C, and sera selected for serogroup C only) for each of the age groups.
    c. Explain the discrepancies between the serologic subsets planned in Table 3.1.1.2 and the reported available serologic data described in Table 3.1.2.2. In your response please include, by immunization group and by serogroup, a description of:
        i. the selection of subsets,
        ii. serum aliquot designation (i.e., were separate aliquots used for each serogroup assay, or were specific samples designated for 1 to 4 different assays depending on the subset allocation),
        iii. criteria for repeat analysis and number of sera that met these criteria,
        iv. sera that were repeated,
        v. results obtained by repeat analysis,
        vi. sera originally selected for initial or repeat assay that were not run,
        vii. sera intended for serologic evaluation for which hSBA data were not available. Please include the criteria used to exclude sera or to designate samples as “no valid result.”

18. In Study V59P13, subjects were enrolled at 44 sites.
    a. Please provide solicited systemic and local adverse events, summary safety and immunogenicity analyses by study site.
    b. There were three centers which enrolled less than 10 subjects. Please explain the reasons for such small enrollments in these centers.
19. The evaluating investigators/study staff of two study sites were prematurely unblinded with respect to vaccine group assignment. Please evaluate whether

these incidents may have had an impact on the study safety results. Also, please submit to CBER a SAS program which would be used for such an analysis.

20. For the sake of the exploratory analysis, please assess the statistical significance of differences in rates of solicited, unsolicited days 1-29, unsolicited days 30-180, and severe local and severe systemic solicited reactions between study groups (on V59P13 Complete Study Report pages page 93, 97, and 100 of 712).
21. In the MenACWY group, 5 subjects reported 8 suicide attempts. Please compare the rate of suicide attempts in this group with the rate for attempted suicide for the general US population. Please comment on the findings.
22. You stated that 18 pregnancies were reported in study V59P13, 15 in the MenACWY group, and 3 in the Menactra group. Of the 15 pregnancies in the MenACWY group, one resulted in miscarriage (08/1006) and four in therapeutic abortion (09/1078, 10/1009, 48/1011, and 54/1003). Of the 3 pregnancies in the Menactra group, one resulted in therapeutic abortion (45/1029) and one in delivery of an infant with hydrocephalus. In the SAE summary, you supplied a clinical summary on the therapeutic abortion only for subject 48/1011 (she was admitted to the hospital for a therapeutic abortion after the demise of the fetus). Please submit the available clinical information on all therapeutic abortions. Please note that some of these adverse events likely should be classified as SAEs. Please comment.
23. In the Clinical Study Report, page 65, you state “None of the subjects withdrew due to an AE.” However, according to the SAE Summary, the father of subject 13/1014 withdrew the subject from the study because she required special care after suicide attempt. Please comment. Additionally, please submit safety profiles of subjects who were vaccinated and prematurely withdrew from the study (82 subjects).
24. In some presentations of your non-inferiority results, you used the statement “superiority criterion met” (e.g., in Clinical Study Report V59P13). Please note that it is unclear how this finding relates to clinical benefit. Moreover, from the statistical point of view, this kind of conclusion is uncertain for study P13. It is still unknown, for example, whether the secondary randomization and assay variability influenced the final results. Therefore, such statements should be removed. Please comment.

**Regarding Study V59P17 entitled A Phase 3, Randomized, Observer-blind, Controlled, Multicenter Study to Compare the Safety and Immunogenicity of Novartis Meningococcal ACWY Conjugate Vaccine with that of Licensed Meningococcal ACWY Conjugate Vaccine (Menactra™) when One Dose is Administered to Healthy Subjects 19-55 Years of Age and with that of Licensed Meningococcal ACWY Polysaccharide Vaccine (Menomune™) when One Dose is Administered to Healthy Subjects 56-65 Years of Age**

25. According to Table 14.1.1.2.1., more study participants were lost to follow-up in the 19-34 year old MenACWY group (12/849) than in the Menactra group (1/470). Please comment.
26. According to Table 14.1.1.4.3, receipt of a DT containing vaccine in the previous 5 years was equally distributed between the vaccine groups. Please assess the effect on safety and immunogenicity associated with having had a DT containing vaccine in the previous 5 years.

**Regarding Study V59P18 entitled Phase 3, Single Center, Open-label, Controlled, Randomized Study to Evaluate the Safety and Immunogenicity of Novartis**

**MenACWY vaccine administered either alone or concomitantly with a Combined Tetanus, Reduced Diphtheria Toxoid, Acellular Pertussis Vaccine (Tdap, Boostrix®) and Quadrivalent Human Papillomavirus [Types 6, 11, 16, 18] Recombinant Vaccine (GARDASIL®) in Healthy Adolescents**

27. Please provide a subset analysis and summary of immunogenicity and safety outcomes by sex.
28. On page 99 of 839 of the P18 Clinical Study Report [Table 12.2.1-1.], it is noted that rates of local, systemic, and other reactions post second dose are all lower than post first dose regardless of study vaccine received. Please comment.
29. Regarding Table 12.2.3-7, over the entire study period, all groups have received the same vaccines. In addition to the summary of all AEs for the entire study period, please evaluate for all study groups the occurrence of "all and possibly related adverse events" by study group by the intervals from first vaccination to the time point of group 2 and 3 second immunization, and from that time-point until the time of 3rd immunization and for 30 days following the group 2 and 3 third immunization.
30. The sero-responses to MenACWY were measured using the hSBA assays and analyzed by serum bactericidal activity geometric mean titer responses (hSBA GMTs). Please:
    a.
        a. Perform additional statistical analysis to evaluate the influence of "Assay" on the testing of the co-primary (#3) non-inferiority immunogenicity hypotheses and the non-inferiority secondary hypotheses that were based on hSBA GMT ratios.
        b. Submit a SAS statistical program that you plan to use for the above mentioned analysis.
        c. Explain why different (hSBA) assay runs were used for different study groups and how sera from Groups II and III were assigned to assay runs.
31. In presentation of results related to the non-inferiority hypotheses, you sometimes stated that the "superiority criterion is met" (e.g., in Clinical Study Report V59P18). Please note that it is unclear how this finding relates to clinical benefit. Moreover, from the statistical point of view, this kind of conclusion is uncertain for study P18. It is still unknown, for example, whether the assay variability influenced the final results. Therefore, such statements should be removed. Please comment.

TOXICOLOGY

32. Please submit a copy of your study report that describes the --b(4)---------- and its findings for -----b(4)----------

LABELING

33. The following comments are regarding vial labeling:
    a. Please spell out the product name in full, and not partially abbreviated.
    b. Please spell out the manufacturer name in full, and not partially abbreviated.
    c. Please present the dosage amount in mL, not ug.
    d. The NDC is missing.
    e. Please add "Rx Only." It is missing.
    f. Please position the trade name under the proper name, not above it.

g. Please ensure the trade name is not more prominent than the proper name.

34. The following comments are regarding carton labeling:
    a. Please add the correct product name on the carton label, as well as throughout the label.
    b. Please reference the package insert on the carton label.
    c. Please add the NDC to the carton label.

We reserve comment on the proposed labeling until the application is otherwise acceptable. We may have further comments when we see the proposed final labeling. The proposed proprietary name, Menveo, has been reviewed and found to be tentatively acceptable. Final acceptability of the name will be determined within 90 days of product approval, when the application is otherwise found acceptable.

We acknowledge that you have included a Pharmacovigilance plan in your BLA and that we have commented on it; however, we reserve our final comments on this proposal for later, when this application is found suitable for approval. Depending on subsequent CBER evaluation and final labeling, CBER may request additions to the Pharmacovigilance plan.

You may request a meeting or teleconference with us to discuss the steps necessary for approval. For PDUFA products please submit your meeting request as described in the FDA Guidance for Industry: Formal Meetings With Sponsors and Applicants for PDUFA Products – February, 2000 (http://www.fda.gov/cber/gdlns/mtpdufa.pdf)(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079744.pdf). For Non PDUFA products, please contact the regulatory project manager. For details, please also follow the instructions described in CBER's SOPP 8101.1: Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants (http://www.fda.gov/cber/regsopp/81011.htm).

Within 10 days after the date of this letter, you should take one of the following actions: (1) amend the application; (2) notify us of your intent to file an amendment; or (3) withdraw the application).

We stopped the review clock with the issuance of this letter. We will reset and start the review clock when we receive your complete response.

If you have any questions, please contact the Regulatory Project Manager, Cara R. Fiore, Ph. D., at (301) 827-3070.

Sincerely yours,

Wellington Sun, M.D.
Director
Division of Vaccines and
Related Product Applications
Office of Vaccines
Research and Review
Center for Biologics
Evaluation and Research