



Our STN: **BL 125363/0**

GlaxoSmithKline Biologicals
Attention: Jody Gould, Ph.D.
Director, North American Regulatory Affairs
2301 Renaissance Boulevard, Building 510
P.O. Box 61540
King of Prussia, PA 19406-2772

Dear Dr. Gould:

This letter is in regard to your biologics license application (BLA) for Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine manufactured at your (b)(4) and Rixensart, Belgium locations and submitted under section 351 of the Public Health Service Act (42 U.S.C. 262).

We have completed our review of all the submissions you have made relating to this BLA with the exception of the information in the amendment dated, June 4, 2010. After our complete review, we have concluded that we cannot grant final approval because of the deficiencies outlined below.

Serological/Statistical Items:

The following items pertain to the *Neisseria meningitidis* serotype Y human bactericidal assay:

1. Because the licensure of this product is based on serology assays only, you must provide scientific evidence showing that the *Neisseria meningitidis* serotype Y (MenY) hSBA assay is validated and is working reliably and consistently. The –b(4)- in titer observed over time, in particular for clinical study MenCY-TT-005, suggest that the assay performance is neither reliable nor consistent. Please provide scientific evidence showing that the *Neisseria meningitidis* serotype Y (MenY) hSBA assay is properly validated for its intended use and is working reliably and consistently. Please provide the following evidence in support of the reliability and consistency of this assay:
 - a. In the “assay development history” document (Module 5.3.5.4.3. GSK hSBA Assay Development History), you indicated that the (b)(4) separate retests of samples from the Hib-MenCY-005 clinical study in a MenY hSBA assay yielded a significant –b(4)----- in titer in the majority of tested samples. You have suggested that this effect may be related to the age of essential serum components of the assay.

Please provide complete data in support of your hypothesis that the proposed changes over time in serum components affect the hSBA titers as observed in the Hib-MenCY-TT-005 study.

- b. Also in the “assay development history” document (Module 5.3.5.4.3. GSK hSBA Assay Development History), you indicate that an additional (b)(4) samples from the Hib-MenCY-007/-008 clinical study were also retested for MenY hSBA and that (b)(4) titers were observed in all (b)(4) samples after retest (GMR 0.5). Please submit the results of the (b)(4) retested Hib-MenCY-007/-008 clinical study sera.
 - c. In a teleconference dated February 9, 2010, you discussed with CBER the possibility that changes in the (b)(4) upon storage might have altered sensitivity in the hSBA assay. Please provide detailed information on the characterization of the MenY strain (b)(4) and any changes it underwent over time. If storage of (b)(4) affects the stability of the assay results as you have suggested, please describe how you will maintain assay stability in the future.
2. In the validation documents for MenC and MenY ELISAs, you have determined “specificity” of the assay by (b)(4). However, the demonstration of (b)(4) is an important aspect of “specificity” determination. Please provide results from (b)(4) performed with heterologous polysaccharide(s).
 3. Regarding the MenY hSBA assay data for the samples from Study Hib-MenCY-TT-013 added as sentinel samples in routine hSBA testing of samples from Studies -009 and -010 (Module 5.3.5.4, pp. 41-42, Table 23), you state that there are (b)(4) samples; however, CBER noticed that there are (b)(4) samples. Additionally, many test results are missing or below the lower limit of quantitation (LLOQ), and the missing values have different codes, e.g., “/,” “IR,” “TC,” or “TD,” without explanations of the codes. Please provide the following information:
 - a. A list of sentinel samples that are excluded and the rationale for the exclusion of sentinel samples in your statistical analysis presented in Table 21 (Module 5.3.5.4, pp. 38-39);
 - b. A definition for all missing value codes;
 - c. An explanation of how test results below LLOQ are treated in your analysis, and an indication of what the “Concordance” values are that are presented in Table 21.

Statistical Items:

The following comments are regarding clinical study Hib-MenCY-TT-009/010:

4. During the pre-BLA meeting you were asked to include in the immunogenicity clinical datasets additional information on the hSBA assays, namely, an assay run identification number for each subject serum. In your SAS “serocod” immunogenicity clinical dataset, this information is missing. Therefore, please resubmit the serology datasets including assay identification numbers. Additionally, please evaluate the influence, if any, the assay run (i.e., the factor “Assay”) has on the estimates of the primary and secondary endpoints related to MenC and MenY. Please submit the SAS statistical program that you plan to use for the above mentioned analysis.
5. With respect to the SAS programs (folder 5.3.5.1.25.3.2, Analysis Program) included in Module 5 of the BLA, the program folder did not contain a sub-folder with “batch” and “macro” sub-folders. To adequately support your statistical results, please submit clear and full documentation on the SAS programs utilized to conduct the statistical analyses referenced in Module 5 of the BLA, and please include all relevant “batch” and “macro” sub-folders.
6. In the primary phase of study Hib-MenCY-TT-009/010, 4441 subjects were enrolled and vaccinated in 91 study centers, and the number of subjects per center ranged from 1 to 800. There were twenty three centers that enrolled less than 10 subjects. Please explain the reasons for the low enrollment in these centers.
7. For the Cohort 1 population, please perform descriptive statistical analyses showing the influence of the factors “race,” “center,” and “gender” on the immune responses (GMTs/GMCs) after the 3rd and the 4th doses of Hib-MenCY-TT vaccine.
8. The Fourth Dose ATP Immunogenicity Cohort (n=521 subjects) does not constitute a subset of the Primary ATP Immunogenicity Cohort (n=695 subjects). There are some subjects in the Fourth Dose ATP Immunogenicity Cohort who are not included in the Primary ATP Immunogenicity Cohort. Please:
 - a. Summarize the reasons why some infants from the Fourth Dose ATP Immunogenicity Cohort were not included in the Primary ATP Immunogenicity Cohort.
 - b. Summarize the reasons why some infants from the Primary ATP Immunogenicity Cohort were not included in the Fourth Dose ATP Immunogenicity Cohort.
 - c. Evaluate the influence of an “indication factor” on GMT or GMC after the fourth dose. The definition of this factor would be as follows: factor is equal to 0 if a subject is in the Fourth Dose ATP Immunogenicity Cohort but he/she is not in the Primary ATP Immunogenicity Cohort; otherwise the factor is equal to 1.

9. With regard to hSBA MenC and MenY titers, please perform statistical analyses to show whether the time elapsed between sera collection and assay run had any influence on the titer after the 3rd dose, before 4th dose, and after the 4th dose of Hib-MenCY-TT vaccination. Please submit a corresponding SAS program with adequate dataset.
10. Objective #4 of study Hib-MenCY-TT-009/010 was to evaluate, using the Fourth Dose ATP Cohort for Immunogenicity data, a “specific” effect of the fourth dose of Hib-MenCY-TT vaccine co-administered with M-M-R II and Varivax at 12 to 15 months of age, namely, “geometric mean of the ratio of the individual post-fourth dose to pre-fourth dose hSBA titers.” Please test the hypotheses related to objective #4 with adjustment for the factors “assay run” and “time elapsed between sera collection and assay run.” Please submit the corresponding SAS program.
11. One of the co-primary objectives was to demonstrate the non-inferiority of Hib-MenCY-TT vaccine as compared to ActHIB (each co-administered with Pediarix) after any dose in terms of the percentages of subjects who experienced fever >39.5°C within the 4-day follow-up period after any dose. You tested this hypothesis based on the pooled dataset from three countries: US, Mexico, and Australia. These countries appear to differ with respect to primary health care and demographic factors. Additionally, over the three-dose vaccination period, at least one concomitant medication (e.g., antipyretic) was used by 72.1% and 75.2% of Hib-MenCY and ActHIB recipients, respectively, during 4 days after each vaccination. Please note that the use of antipyretic medication is correlated with occurrences of fever events. Thus, it appears that distributions of fever events by study group alone may not supply unbiased results. Therefore, please retest this hypothesis utilizing longitudinal, mixed effects logistic models (e.g., Geert Molenberghs and Geert Verbeke, 2004, Meaningful Statistical Model Formulations for Repeated Measures, *Statistica Sinica* 14; Dimitrienko, A., Molenberghs, G, Chuang-Stein C. and Offen, W., “Analysis of Clinical Trials Using SAS®: A Practical Guide”) adjusting for factors “country” and “use of concomitant medication.” Please submit the SAS program used for this problem.
12. For any occurrence of grade 3 unsolicited symptoms (Primary Total Vaccinated Cohort), please perform statistical analyses utilizing longitudinal, mixed-effects logistic models (e.g., Geert Molenberghs and Geert Verbeke, 2004, Meaningful Statistical Model Formulations for Repeated Measures, *Statistica Sinica* 14; Dimitrienko, A., Molenberghs, G, Chuang-Stein C. and Offen, W., “Analysis of Clinical Trials Using SAS®: A Practical Guide”) adjusting for the factors “use of concomitant medication” and “country.” Please submit the SAS program used for this problem.

Clinical Items:

13. We note your inclusion of the sensitivity analyses with and without the safety data from Dr. Naz's site (studies Hib-MenCY-TT-009 and Hib-MenCY-TT-010). Please clarify how safety data were categorized by treatment assignment for the sensitivity analyses given that one reason for excluding Dr. Naz's site data was inability to confirm treatment assignment.
14. In study Hib-MenCY-009 Table 12, we note that 2898 MenHibrix recipients and 955 Hib recipients in the Total Vaccinated Cohort (TVC) completed the extended safety follow-up (ESFU). However, fewer TVC MenHibrix (n=2888) and Hib (n=961) recipients completed the safety follow-up through one month post-dose 3 (table 11). Please explain why the number of vaccinated participants completing the ESFU is greater than the number of participants who completed the primary active phase.
15. Please clarify if the eleven Hib-MenCY-TT-009 subjects (n=10 MenHibrix, n=1 Hib) who withdrew or prematurely discontinued from the study completed the ESFU.
16. Please clarify in study Hib-MenCY-TT-011, during the period from day 0 after dose 1 through day 30 after dose 3, the number of subjects in each treatment group reporting Adverse Events (AEs) leading to ER visits and the number of reported events of this nature.
17. Regarding subject 04863, the 10 month-old U.S. male in study Hib-MenCY-TT-009 with family and personal history of developmental delay who developed seizure 5 months post-dose 3 of the study vaccines, the serious AEs (SAEs) narrative first states that Hib-MenCY was given but later states that ActHIB was given. Please clarify which study vaccines the subject received.
18. Please provide a clinical summary and table describing the reported occurrence of SAEs, new onset chronic diseases (NOCD), rash, and AEs resulting in ER visits for study Hib-MenCY-TT-009 within 30 days of vaccination. The table should include the number and percentage of subjects reporting these events, with 95% confidence intervals for each treatment group, and the relative risk (HibMenCY-TT/Hib), with corresponding 95% CI.
19. Regarding the dataset for the MenACWY-TT-057 study submitted to the BLA, please provide a clinical summary for subject 057-2762, date of birth ----(b)(6)-----, who appears to have developed poor muscle tone 21 days post-vaccination with Hib-MenCY-TT.
20. Please send a detailed case summary for subject (b)(4) 7420 with coronary artery fistula (study Hib-MenCY-TT-012). Please confirm that this is the same subject as ----(b)(4)-----
-----.

Items Regarding the Chemistry, Manufacturing and Control (CMC) Information:

The following items refer to sections in the submission where the description of the manufacturing process is inadequate or incomplete or the manufacturing process and testing have not been completely validated:

General

- 21. Please provide information specifying how the date of manufacture is defined with respect to the expiration dating period for MenHibrix and the sterile diluent manufactured by GSK.
- 22. We note that you refer to multiple GSK monographs throughout the CMC Modules of the BLA; however, you have not provided these monographs for review. Please submit all GSK monographs related to CMC of MenHibrix which you have referenced in this BLA.
- 23. We note that during manufacture of MenHibrix, you have tests that are classified as monitoring, Quality Decision, or Quality Release tests. Please provide detailed information regarding how an OOS result for each of these test classifications is handled. For example, please specify how you determine if and when it is allowable to perform an investigation and still use the product.

Regarding the Tetanus Drug Substance:

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

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

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

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

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

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15 Pages determined to be not releasable: b(4)

67. Please add the following as QC Release Tests for the MenHibrix final container (Module 3.2.P.5.1):

- a. -----(b)(4)-----;
- b. ---(b)(4)----;
- c. -----(b)(4)-----;
- d. -----(b)(4)-----;
- e. -----(b)(4)-----;
- f. ----(b)(4)-----
- g. ----(b)(4)---

68. ---(b)(4)--- level assessment is included as a QC release specification during different stages of manufacture. You indicate that your proposed ---(b)(4)--- level specifications are based on data obtained during process validation. However, we note that for each of these stages of manufacture the ---(b)(4)--- specifications exceed the actual values obtained during process validation by approximately a factor of (b)(4). Please revise each of the following proposed specifications to be reflective of actual validation data:

- a. In Module 3.2.S.2.4, the ---(b)(4)--- level specification for *N. meningitidis* Serogroup C Polysaccharide is “not more than -----(b)(4)-----”. However, the batch analysis data show that ---(b)(4)--- batches have an ---(b)(4)--- level of less than -----(b)(4)----- and the remaining batch has an -----(b)(4)--- level of -----(b)(4)-----. Please revise your proposed specification to be reflective of actual validation data.
- b. In Module 3.2.S.2.4, the ---(b)(4)--- level specification for *N. meningitidis* Serogroup Y Polysaccharide is “not more than -----(b)(4)-----”. However, the batch analysis data show that ---(b)(4)--- batches have an ---(b)(4)--- level of less than -----(b)(4)----- and the remaining (b)(4) batches have an ---(b)(4)--- level of -----(b)(4)-----. Please revise your proposed specification to be reflective of actual validation data.
- c. In Module 3.2.P.5.1, the endotoxin level specification for MenHibrix final product is “not more than ----(b)(4)-----.” However, the batch analysis data show that the endotoxin levels are always less than ----(b)(4)-----. Please revise your proposed specification to be reflective of actual validation data.

69. In Module 3.2.P.2 you indicate that the free polysaccharide content test by (b)(4) is not accurate. The (b)(4) method was used for testing and release of conjugate bulks and final product for the clinical consistency lots. The free polysaccharide contents assessed by

chemical methods (---(b)(4)--- for Hib-TT, (b)(4) for MenC-TT, ---(b)(4)--- for MenY-TT) are proposed to replace the (b)(4) based method at the level of the conjugate bulks. -----(b)(4)----- is proposed to replace the (b)(4) based method on drug product. Please address the following with respect to the free polysaccharide content:

- a. Appropriate validation studies should be performed to change the free polysaccharide methods. For Hib-TT, data comparing Free Hib by --(b)(4)-- and -----(b)(4)----- was provided in the BLA for (b)(4) commercial consistency lots (Module 3.2.S.2.3). If available, please provide data from any additional lots to demonstrate that these two methods are equivalent.
 - b. In Module 3.2.S.7.3, you provide stability data for commercial bulk conjugate lots. We note that there is a decrease in free polysaccharide C content by (b)(4) between your time-zero testing and the -----(b)(4)----- time points. We also note that there is an increase in free polysaccharide Y content by ---(b)(4)--- between your time-zero testing and the -----(b)(4)----- time points. Please provide an explanation for these results and the variability in your assays.
 - c. The specifications for free polysaccharide are not changed with the change in method for Hib-TT or MenC-TT. However, the specification for MenY-TT changed from not more than ----(b)(4)---- with the change in method from -----(b)(4)----- . We do not concur with this change in specification. Please revise your specification for free polysaccharide by ---(b)(4)--- for MenY-TT to not more than (b)(4).
 - d. The proposed -----(b)(4)----- also uses an (b)(4) based method. Please justify the use of this method based on your observation that the (b)(4) method is not accurate.
 - e. All clinical lots were released using the (b)(4) based method. Please explain the effect on your clinical studies of using an inaccurate release method.
 - f. You propose to (b)(4) the free polysaccharide by -----(b)(4)----- for drug product. Please provide quantitative data demonstrating that -----(b)(4)----- can accurately measure free polysaccharide for Hib, MenC, and MenY in the final drug product.
 - g. Please provide stability-indicating validation data that demonstrate that the -----(b)(4)----- assays can accurately quantify the decrease in free polysaccharide due to degradation of product.
70. In Module 3.2.P.5.2, you provide the polysaccharide content specifications for MenHibrix final product. Please revise your polysaccharide specifications as follows:
- a. The proposed specification for Hib content for MenHibrix is not less than (b)(4) of the target value. Please revise this specification to between --(b)(4)--- per dose.

- b. The proposed specification for Total –(b)(4)--- content for MenHibrix is not less than (b)(4) of the target value. Please revise this specification to between -----(b)(4)- per dose.
 - c. The proposed specification for Total (b)(4) content for MenHibrix is not less than (b)(3) of the target value. Please revise this specification to between –(b)(4)-- per dose.
 - d. The proposed specification for Total PSC content for MenHibrix is not less than (b)(4) of the target value. Please revise this specification to between ----(b)(4)----- per dose.
71. In Module 3.2.P.5.1, you provide the QC Release Specifications for MenHibrix final product. Please specify which diluent (GSK or (b)(4)r) you will use to reconstitute product prior to performance of release testing. For example, please specify if both the GSK and (b)(4) diluents will be used for reconstitution of the MenHibrix final product prior to release testing or if only one of the diluents will be used.

Regarding Drug Product Hold Times and Stability:

72. In Module 3.2.P.3.5 (Process Validation and/or Evaluation – Hib MenCY-TT), you propose a hold time of -----(b)(4)----- . However, you only have data from (b)(4) commercial lot that was held for (b)(4). We do not agree that hold time data for your development lots are sufficient to support your proposed (b)(4) hold time due to the manufacturing changes that occurred over the product development process. Please provide data from (b)(4) additional commercial lots held for (b)(4) to support this hold time.
73. In Module 3.2.P.8.3 (Stability Data, Hib-MenCY-TT), you note that the stability results for -----(b)(4)----- show a slight decrease over time. You indicate that in Tables 14 and 15 of this Module for (b)(4) MenC-TT and (b)(4) MenY-TT, ---(b)(4)----- were used after the –(b)(4)--- time point. You propose that the variability of the method is mainly due to the variability of the --(b)(4)-- used and that use of a ----(b)(4)----- at these time-points seems to introduce a bias towards a decrease in (b)(4) for MenC-TT and MenY-TT. Please address the following with respect to the decrease in (b)(4):
- a. Your explanation that a –(b)(4)-- change is responsible for a decrease in the (b)(4) is inadequate. If the method and --(b)(4)- were properly validated and qualified, a decrease in (b)(4) should not have been seen as a result of a --(b)(4)- change only. Please explain.
 - b. As described previously, you provide (b)(4)- characterization data which show inconsistencies in the (b)(4) between the commercial and clinical lots. These data demonstrate that the molecular weights of the conjugates can vary widely. Please provide any available data for validation of the (b)(4)- assay.

- c. You indicate that from currently available data, a decrease in molecular weight (MW) cannot be ruled out. Please provide an explanation of the impact of the potential decrease in MW for product stability and consistency.

74. In Module 3.2.P.8.2 (Post-approval Stability Protocol and Stability Commitment - Hib-MenCY-TT), you provide data from stability studies of commercial drug product performed in support of the BLA and a protocol for on-going stability studies of commercial drug product post-approval. Please address the following with respect to these studies:
 - a. Please include free polysaccharide (Hib, MenC, and MenY) content in your current stability studies and your protocol for future on-going stability studies.
 - b. We do not agree with your plan to assess polysaccharide content (Hib, MenC, and MenY) at only the time -----(b)(4)----- time points for your current stability studies. Please revise your current stability studies and your protocol for future on-going stability studies to include assays to assess polysaccharide content (Hib, MenC, and MenY) at each time point.
 - c. Your specification for -(b)(4)---- content is listed as not more than ----(b)(4)----- Please revise this specification to be reflective of actual data obtained in your process development studies. In addition, please revise your protocol for on-going stability to include -(b)(4)----- testing at each time point.

75. In Module 3.2.P.8.2.3 (Stability), you provide stability data in support of reconstituted drug product. This stability study did not evaluate pH or free polysaccharide (Hib, MenC, and MenY). Please repeat this study evaluating these additional parameters. In addition, in Module 3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment (Hib-MenCY-TT), you do not propose to perform reconstitution studies as part of your routine on-going stability studies. Please provide a plan/protocol to perform on-going annual stability studies on reconstituted drug product. Please specify in your plan how you will incorporate both diluents manufactured by GSK and by -----(b)(4)-----

76. In Module 3.2.P.8.2.3 (Stability, Hib-MenCY-TT), you propose an expiration date of 36 months for final filled drug product (page 4). You base your proposed expiration date on data from studies on clinical products and 6 months of real-time data with commercial drug product. Due to significant manufacturing changes between the clinical development lots and the commercial consistency lots, the data from the clinical lots are not fully supportive of your proposed expiration dating for commercial product. Your expiration dating will be based on real-time stability accrued for your commercial stability lots. Please acknowledge.

77. Regarding Module 3.2.P.8.2.3 (Stability, Hib-MenCY-TT), please provide a protocol to perform on-going annual stability studies on (b)(4) lot of Hib Polysaccharide, MenC Polysaccharide, MenY Polysaccharide, Purified Hib-TT Bulk Conjugate, Purified

Meningococcal Group C Conjugate Bulk, and Purified Meningococcal Group Y Conjugate Bulk per year. The bulk lot chosen for stability evaluation should be different from the lot which is used to manufacture the MenHibrix final container placed on stability.

78. In Module 3.2.P.8.2 (Post-approval Stability Protocol and Stability Commitment - Diluent), we note that you have made the following changes to your proposed on-going stability study protocol for the 0.9% Sodium Chloride diluent: volume, particle count, chloride identity, and sodium identity have been deleted from the protocol. Please provide a justification for these proposed changes.
79. In Module 3.2.P.8.2.3 (Stability Data, Diluent), you propose a –(b)(4)-- expiration date for the 0.9% Sodium Chloride diluent based on stability collected with a different plunger stopper and different sterilization process than is currently used for the manufacturing of the diluent. Please revise your expiration dating for the diluent to be reflective of stability data collected on diluent manufactured with the current manufacturing process and container/closure system for the diluent (i.e. –(b)(4)--). If you have additional data with diluent manufactured with the current manufacturing process, please submit these data for review.
80. In Module 3.2.P.5.4, you provide batch analysis data for 0.9% sodium chloride diluent manufactured using the current process. It appears as if these are different fills of the same batch. Please confirm. If this is the case, please provide additional batch analysis data from different batches of diluent.

Regarding Amendment 3 and the CMC Information for Inclusion in the Package Insert:

81. In Amendment 3 dated February 12, 2010, you provide revisions to multiple data tables (e.g., stability data values, batch analyses data values, QC test values). Please provide a complete explanation of the source of these errors reported in the data tables. For example, please explain whether these are data transcription errors, calculation errors, or other types of errors. In addition, please describe at what level the error occurred (manufacturing, quality department, preparation of batch records, testing laboratories, etc.) and any related investigations and corrective actions taken as a result of the errors.
82. In Amendment 3 dated February 12, 2010, you state that any changes in reference material for Hib-TT, MenC-TT, MenY-TT, and Hib-MenCY-TT testing would be communicated to the agency in your Annual Report. We would need a detailed CP in order for reference material changes to be reported annually. Please submit a detailed CP or alternately, submit a detailed CP as a PAS after licensure.
83. The package insert states that MenHibrix should be administered within –(b)(4)--- of reconstitution. Also, the package insert states that after reconstitution, the vaccine should be stored refrigerated or at “controlled room temperature between 2 and (b)(4)--. You do not have sufficient data to support storage of the reconstituted vaccine at (b)(4). Please

remove the statement regarding “storage at controlled room temperature between 2 and (b)(4)-” from your package insert.

Regarding the Varicella Serology Assay:

84. You have not demonstrated that the (b)(4)- anti-varicella assay results are free of bias. Specifically, you have not provided information showing that the technicians who performed the assays for this study were capable of providing consistent (b)(4)- readings, you have not shown that technicians who performed the assays were masked as to treatment group, and you have inconsistently applied a cutoff (b)(4) in some places, (b)(4) in other places) for this assay. Moreover, this assay appears to possess high background (in Clinical Study 008, an unusually high number, more than 23% of varicella vaccine naïve subjects were varicella seropositive in the MenHibrix pre-booster groups), making results difficult to interpret. Until these deficiencies are addressed, it cannot be concluded that MenHibrix does not interfere with anti-varicella vaccine responses.
- a. In your response to a previous FDA comment Item # 10 regarding (b)(4)--- validation study in a CBER letter dated October 30, 2007 ("Please describe the basis on which samples to compare the specificity of the various assays were selected. Was this study performed under a prospectively determined protocol? If so, please provide the protocol." Page 14 appended to the (b)(4) SOP), you did not provide the standard protocols or SOPs for the (b)(4), GSK's ----(b)(4)---- and ---(b)(4)----- assays. Please provide SOPs or protocols for the IFA, GSK's ----(b)(4)----- and ---(b)(4)----- assay to support the results from these assays.
 - b. Please provide information regarding whether the clinical samples were handled in a blinded manner when using (b)(4) to detect ---(b)(4)---- antibody, and how many technicians were directly involved in the analysis of samples by (b)(4).
 - c. In Clinical Study 008, more than 23% (23.6% - 31.6%) of subjects were varicella seropositive in the Pre Booster groups (with anti-Varicella titers more than (b)(4) based on (b)(4)----. This number is higher than previously published experience for children 1 to 1.5 years of age without previous varicella exposure or varicella vaccination, and suggests some level of assay artifact. Please explain.
 - d. The submission indicates that the Cut-Off for (b)(4) was changed from (b)(4) to (b)(4). However, in many parts of the submission, the Cut-Off is still labeled and used as (b)(4). Please correct or clarify this apparent discrepancy or justify why two Cut-Offs are needed.

Facilities Items:

85. We acknowledge that you have submitted the method validation study for container/closure integrity testing for vials and –b(4)---- used for MenHibrix and its diluent –b(4)----- . Please provide the results of container/closure integrity testing for the lyophilized product and diluent manufactured at your Belgium facility. Please note that for the proposed (b)(4) diluent filling line, we recommend container/closure integrity testing be performed initially to validate the integrity of the package design and at the ----(b)(4)----- of the product shelf life as part of the packaging stability program.
86. Regarding visual inspection of your diluent –b(4)----- (filled at GSK), we acknowledge that you have provided validation for –b(4)---- tip-cap orientation, fill volume, and particulates. We also acknowledge that you have provided summary data for the (b)(4) most recent aseptic simulation runs for the (b)(4) diluent filling line with reject data. Please provide the validation of the 100% visual inspection with regards to container and closure defects. You should provide definitions of Critical, Major, and Minor defects with a rationale for how each type of defect was defined and the AQL/acceptance criteria for each type of defect. The validation should also cover inspector qualification and training. Finally, please provide the results of the 100% visual inspection for the diluent for the –b(4)----commercial lots of MenHibrix.
87. Regarding shared equipment of the diluent fill line, (b)(4), please provide a description of how product-contact equipment is cleaned. In addition, please provide a summary of the validation data to support cleaning procedures.
88. According to the information provided, the TT and polysaccharide conjugate bulks are -----(b)(4)----- . Please provide validation summaries for each of the ----(b)(4)----- used in these processes.

We reserve comment on the proposed labeling until the application is otherwise acceptable. We may have comments when we see the proposed final labeling. The proposed proprietary name, Menhibrix, 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.

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.

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.

You may request a meeting or teleconference with us to discuss the steps necessary for approval. Please submit your meeting request as described in our “Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants,” dated May 2009. This document is available on the internet at

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/default.htm> or may be requested from the Office of Communication, Outreach, and Development, at (301) 827-1800. 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. This document also is available on the internet at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079448.htm>, or may be requested from the Office of Communication, Outreach, and Development.

Please be advised that, as stated in 21 CFR 601.3(c), if we do not receive your complete response within one year of the date of this letter, we may consider your failure to resubmit to be a request to withdraw the application. Reasonable requests for an extension of time in which to resubmit will be granted. However, failure to resubmit the application within the extended time period may also be considered a request for withdrawal of the application.

We acknowledge receipt of your amendment dated June 4, 2010. Please be aware that we have stopped the review clock with the issuance of this letter. We will reset and start the review clock when we receive your complete response. You may cross reference applicable sections of the amendment dated June 4, 2010 in your complete response to this letter and we will review those sections as a part of your complete response.

If you have any questions regarding the above, please contact the Regulatory Project Manager, CDR David Staten, at (301) 827-3070.

Sincerely yours,

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