



Our STN: **BL 125363/0**

GlaxoSmithKline Biologicals
Attention: Jody Gould, Ph.D.
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 (MenHibrix) 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. After our complete review, we have concluded that we cannot grant final approval because of the deficiencies outlined below. Please note that each “Item” indicated in the comments below is in reference to the Complete Review letter dated June 11, 2010.

Regarding the *Neisseria meningitidis* serotype Y human bactericidal assay:

1. In response to Item 1a, you indicated that study 005 sera were not handled according to the SOP. You indicated that the study 005 -----
 --- (b)(4) -----, which is significantly more than the ----- (b)(4) ----- . You hypothesized that ----- (b)(4) ----- cycles may have led to ----- (b)(4) ----- . You then tested this hypothesis by retesting immune sera subjected to ----- (b)(4) ----- in the hSBA. The results of your ----- (b)(4) ----- cycles experiment showed that the assay is robust for up to --- (b)(4) --- and there may be a small impact --- (b)(4) --- . Thus, these data do not support your hypothesis that the observed --- (b)(4) --- in MenY titers is attributable to excessive ----- (b)(4) ----- . In addition, you have also suggested that the (b)(4) of the study 005 sera may have played a role in the --(b)(4)-- of hSBA titers, but you have not tested this hypothesis and have not established the storage time-point at which hSBA titers begin their decline. We conclude that the reasons for the --(b)(4)-- in study 005 hSBA titers remain unknown. Please provide any additional information you may have that would explain the --(b)(4)-- in study 005 hSBA results.
2. In response to Item 1b, you presented a table of reference and retest hSBA values for selected samples (Table 2) tested in the Y assay. We note that the retesting of these samples demonstrated a lower value in the retest for 11 of the 14 samples. Nine of the

14 retest hSBA values are greater than two-fold lower than the reference values and two of the 14 retest hSBA values are greater than or equal to four-fold lower than the original values. Thus, these data do not support the stability of the hSBA for the Men Y over time.

In response to Item 3a, you provided data relevant to the reliability of the hSBA for Men Y. Specifically, you presented a table of hSBA values from the Y assay for the sentinel samples included in study HIB-MENCY-TT-013 (Table 5). We note that seven out of 50 samples show a greater than four-fold discrepancy between the highest and lowest reported values. Four samples show results both above and below a titer of (b)(4), including one sample with a titer in the -----(b)(4)----- . The samples with only one replicate provided are not included in the totals. In addition, a substantial amount of data is missing from the table which precludes a complete assessment of assay stability.

Together, the ---(b)(4)--- titers seen in the repeat analyses for samples from Study Hib-MenCY-005 (refer to item 1 above), in conjunction with the ---(b)(4)--- titers and the discrepancies in the data submitted in response to Items 1b and 3a (refer to item 2 above), raise concerns with regard to the ability of the hSBA assay for the Y strain to produce reliable and consistent data over time. While it is acknowledged that sample -(b)(4)- may have been one factor leading to --(b)(4)-- hSBA titers in the Men Y retest, adequate control of the assay during the sample analysis of the pivotal studies is critical. In this regard, we request the following additional information:

- a. To evaluate whether small changes in the assay over time would have affected all groups from a given study equally, please provide the blinding and randomization scheme for analysis of the samples from the pivotal studies.
- b. Given the apparent instability of the hSBA for the Y strain, please address the following:
 - i. Please provide data that demonstrate that the ----(b)(4)---- algorithm maintains consistent assay performance across changes in control and complement lots. Please provide a trending analysis for the ----(b)(4)---- values that demonstrates consistent assay performance within control and complement lots. Please show that the ----(b)(4)---- algorithm is independent of sample titer, i.e., that the variance of the -----(b)(4)----- ratio is constant relative to titer.
 - ii. Please present the analysis that demonstrates that the four-parameter model can be appropriately fitted to the bacterial count data generated in the assay. Please describe how the a and d parameters for each sample are determined and controlled. Please comment on whether the curve fitting is constrained, and if so, please explain how it is constrained. Please provide the basis for the criterion that each sample has an R^2 greater than 0.85.

- iii. You presented quality control charts for positive controls in the MenY hSBA assay (QC1 and QC2) for the testing period from July 2009 to June 2010 to demonstrate assay stability. We notice that in the QC chart for Control 1 (-----b(4)-----) for the period from July 2009 to January 2010 (Section 4.3.8, Figure 2, page 30), many data points are below the lower limit. For the period from February 2010 to June 2010 (Section 4.3.8, Figure 3, page 30), the target value for Control 1 (-----b(4)-----) is changed to a higher level. Although all data points are within the control limits, the range between the lower and upper control limits becomes much wider. In light of these observations, please explain why you conclude that the hSBA MenY assay is stable.
 - iv. The time period covered by these QC charts (July 2009 to June 2010) began several months after the testing of samples from studies 009 and 010 (Jan 2009 to February 2009) was completed. Thus, these QC charts do not provide information regarding the assay stability at the time the testing of samples from the clinical studies supporting this BLA was performed. Please provide data that support the stability of the assay covering the actual testing period from study -005 to study -010. Data that would be supportive include all QC charts for controls with trending analyses, reagent qualification data for any new controls or complement introduced during the analysis of samples from a given study, and all sentinel data. A detailed and continuous time line depicting the changes in controls and complement lots during the entire testing period should also be included.
3. We are concerned that missing data for the samples from Study -013 added as sentinel samples in routine hSBA testing of samples from Studies -009 and -010 may have biased the results of the Men Y assay stability evaluation, especially for week 1. Out of the b(4) samples tested in week 1, only 20 samples have valid titer results. Eight samples have a missing value code “TC”, meaning that they were supposed to be retested at a lower dilution because less than 2 dilution points of the curve have $\geq 50\%$ killing. Since these missing TCs are not missing at random, excluding these samples could make the GMR at week 1, relative to the initial reference, higher than the true ratio had those TC samples been re-tested (based on their titers at weeks 2-4). Overall, the GMRs during the four weeks clearly suggest that a -b(4)--- in MenY titers from the initial reference values is also present for these sentinel samples from study -013. Also, the concordance analysis may not be useful for evaluating this unidirectional (-(b(4)--)) assay stability issue and its potential impact on the clinical studies results, because there are many samples with titers < 4 initially and few samples near the cutoff point. Please comment.

Regarding General CMC Information:

- 4. The Comparability Protocols (CPs) provided in response to Item 82 for changes in reference standards are inadequate for the purposes of reporting such changes in your Annual Report. Please address the following deficiencies in the CPs:
 - a. Most of the CPs have acceptance criteria of less than 10% differences in results generated with new and old reference standards. However, the CPs for the Free TT Content and Identity assays contain qualification criteria stating that comparability between the old and new standard is demonstrated if the results are $\pm 30\%$. Such a large variability in the calibration of new standards is not acceptable. Please revise the criteria for calibrating new standards for the Free TT Content and Identity assays.
 - b. Even 10% differences between new and old reference standards can cause problems, particularly when qualifying a new reference standard against the current standard multiple times over the life of the product. A new standard should be calibrated against the original or primary standard to avoid drift away from original value. Please develop a primary reference standard for each assay to avoid drift in calibration of reference standards over the life of the product.
 - c. The number of qualification runs varies depending on the assay. Please run a minimum of (b)(4) qualification runs for each assay.
 - d. The number of samples run (Internal control run alone or Internal Control run with another sample) varies depending on the assay. Please run the Internal Control and (b)(4) lots of product to qualify a new lot of reference standard for each assay.
 - e. Some of the CPs contain acceptance criteria for assay validity and some do not. Please include assay acceptance/validity criteria as part of all CPs. Please specify in the qualification criteria that both the old and new standards must meet assay acceptance/validity criteria.
 - f. The CPs for Identity by (b)(4) for Hib-TT in conjugate bulks and MenHibrix FC state that the reference is final container Hib. Please confirm that “Hib” refers to Hiberix.

Regarding Drug Substance Manufacture:

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

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

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

Regarding Drug Product Specifications and QC Release:

- 15. We do not concur with your proposal to not add ----(b)(4)---- as a QC Release test for Final Container MenHibrix. Please assess ----(b)(4)---- as a QC Release test.
- 16. We note that you calculated the --(b)(4)-- specification based on pooled data from *Neisseria meningitidis* polysaccharides (b(4), C, b(4), and Y). However, the calculation of --(b)(4)-- specifications should be serotype specific. In addition, the ---(b)(4)--- specification for Drug Product should be process capability driven and should reflect actual process data. Please re-calculate your ---(b)(4)--- specification to be reflective of actual process data for each serotype individually.

Regarding Drug Product Hold Times and Stability:

- 17. We do not concur with your proposal to not assess polysaccharide content (Hib, MenC, and MenY) during on-going stability studies of commercial drug product. Please revise your protocol for future time points in on-going stability studies to include assays to assess polysaccharide content (Hib, MenC, and MenY) at each time point.
- 18. Please provide written procedures to ensure that all licensed, commercially distributed diluents are represented during reconstitution during MenHibrix stability testing.
- 19. We do not concur with a --(b)(4)-- shelf life for MenHibrix as proposed in the BLA. Please revise the expiration date to reflect the real time stability data (i.e., --(b)(4)--).
- 20. Please add sterility testing to the annual stability protocol of Hib-TT. Also, please add sterility and --(b)(4)-- testing to the annual stability protocol of MenC-TT and MenY-TT.
- 21. We do not concur with your proposal to not place (b)(4) lot of polysaccharide purified bulks on stability per year. Please revise your procedures to include placing (b)(4) lot of polysaccharide purified bulks on stability per year.

Regarding Specifications and Analytical Methods Validation:

- 22. In response to Item 42a, you provided the validation report rppt-9000001149RVM004, which concluded that the -----(b)(4)----- will be compensated for by multiplying final results by a (b)(4) factor. A previously calculated LOQ of (b)(4) micrograms/mL is now assigned (b)(4) micrograms/mL. It is stated that "all lots where no -(b)(4)- content is detected will be reported as below (b)(4) micrograms/mL". The lowest standard described in the procedure (SOP 9000001149 V2) is (b)(4) micrograms/L. This

approach will be satisfactory if the assay is classified and implemented as a limits test rather than a quantitative procedure. We have the following additional requests:

- a. Classify the procedure as a limits test rather than a quantitative impurities procedure.
 - b. Since the lowest standard is (b)(4) micrograms/L, please report results as (b)(4) micrograms/L when applying the bias correction. Please modify the product specification to (b)(4) micrograms/L.
 - c. Clarify that the LOQ stated in the conclusion is micrograms/L not micrograms/mL.
23. In response to Items 42c, 42e and 42g with regard to the linearity of the method for measuring free PS you stated in Report 9000000693 RVM010, Section 3.4 that “theoretical concentrations were calculated by taking the mean of the experimental concentrations (mean of the individual values from 4 independent series)”. Thus, experimental results are used to establish the theoretical concentrations and then the same results were compared to the theoretical concentrations. This is not acceptable to measure assay linearity as it creates a circular argument.

We suggest that data already generated to support precision and accuracy could be used to demonstrate the linearity of these methods. For example, accuracy has been demonstrated by (b)(4) of samples with PRP saccharides at (b)(4) concentration levels and (b)(4) replicates at each level. Please re-analyze these data in Report 9000000693 RVM010 Section 3.6 to demonstrate linearity of Free PS method for Hib-TT bulk conjugate. Similarly, please re-calculate linearity of Free PS methods for MenC-TT and MenY-TT Bulk Conjugates.

24. In response to Item 53 regarding the (b)(4) of MenC-TT and MenY-TT Bulk Conjugates by (b)(4) (SOP 9000006776), you provided the criteria for (b)(4) selection and validation documents. Please provide the following information from the validation study:
- a. In the validation report, there are (b)(4) lots of (b)(4) Y tested. Please provide a description of the (b)(4) Y sample and the relevancy of this sample type to the product. It is stated that the unusual high recovery (b)(4) of (b)(4) Y is still under investigation. Please provide a copy of the final investigation report to include determination of the root cause for this discrepancy.
 - b. The test result of Hib FC-lot (b)(4), which is listed as a sample in page ‘16 of 32’ of the validation protocol, cannot be found in the validation report. Please submit the test result for this sample or provide a reason as to why it was not included in the validation report.
 - c. Please submit an SOP for (b)(4) determination of Bulk Conjugates with the (b)(4) to replace SOP 9000001926.

25. In response to Item 67a, you provided a validation report for the sucrose method. The evaluation of linearity for this method by (b)(4) in the validation report 9000011398RVM001/01/01 is described as being applied to “standards solutions” and “evaluated by establishing a linear regression model between the back-calculated concentrations and the theoretical concentrations ...”. It is unclear whether the “standards solutions” represent calibration standards or “validation standards” in placebo matrix as described in Section 1.1. The meaning of “back-calculated” is unclear, but appears to be a circular calculation of these standards against themselves. However, the data presented in Sections 1.2 “Response function” and 1.7 “Specificity” adequately support linearity across the range of the method for both calibrants and analyte in placebo matrix. If these data are suitable, please re-analyze these data to demonstrate linearity for this test method.

Regarding Facilities:

26. During the June 30, 2011 teleconference, you indicated that you will provide a detailed diluent inspection protocol describing how the -----(b)(4)----- is used in combination with a manual visual inspection. You also indicated that you plan to perform full manual visual inspection in conjunction with the (b)(4) and submit the manual inspection data for the first lot of diluent filled at your Belgium facility. To date we have not received the protocol or results of this inspection. Please submit the protocol and the resulting data.

We reserve comment on the proposed final labeling until the application is otherwise acceptable. The proposed proprietary name, MenHibrix, has been reviewed and found to be tentatively acceptable. Please note that 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 we have provided initial comments. However, final comments and/or requests for revisions of your Pharmacovigilance plan will be provided at the time that this application is found suitable for approval.

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.

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 September 20, 2011. You may cross reference applicable sections of the amendment dated September 20, 2011, 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 Managers, CDR David Staten or Kirk Prutzman, Ph.D., at (301) 796-2640.

Sincerely yours,

Wellington Sun, M.D.
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