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To: File, STN 125363/12

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Subject: Serology Review Memo for BLA 125363/12 (MenHibrix)

Sponsor: GlaxoSmithKline (GSK)

APPROVED
By Mustafa Akkoyunlu at 3:04 pm, Aug 25, 2011

APPROVED
By Freyja Lynn at 3:09 pm, Aug 25, 2011

APPROVED
By Willie F. Vann, Chief LBP at 4:38 pm, Aug 25, 2011

APPROVED
By Jay Slater at 5:00 pm, Aug 25, 2011

Submissions Reviewed

MenHibrix is a non infectious vaccine that contains *Neisseria meningitidis* serogroup C capsular polysaccharide, *N. meningitidis* serogroup Y capsular polysaccharide, and *Haemophilus influenzae* type b capsular polysaccharide (polyribosyl-ribitol-phosphate, PRP), each individually covalently bound to tetanus toxoid. The vaccine is to be reconstituted prior to intramuscular injection, with a liquid saline diluent supplied in –b(4)----- containing (b)(4) of diluent. The reconstituted product contains 2.5 µg of PRP-TT, 5 µg of PSC-TT, and 5 µg of PSY-TT per 0.5 ml dose volume. The proposed indication is for active immunization of infants and toddlers 6 weeks through 15 months of age for the prevention of invasive diseases caused by *N. meningitidis* serogroups C and Y and *H. influenzae* type b.

An eighty-eight item CR letter was issued on 11 June 2010. There were two multi-part questions regarding serology in the CR letter. Serology is a matter of primary concern for this vaccine as its approval is based solely on serology endpoints. GSK provided their response to the CR letter on 15 April 2011. This memo summarizes review of the firm's responses to serology items 1 and 2. The following documents were reviewed:

- Module 1.11.3 CRL June 10-Efficacy Response to CBER hSBA MenY
- Module 1.11.3 CRL June 2010-Efficacy Questions 1-20. 84.
- Module 5.3.5.4.3 Validation report 2009-V-008
- Module 5.3.5.4.3 Validation Protocol 2009-V-008

Question 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 (b)(4) 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.

Explanations provided for the--(b)(4)-- in retested study 005 sample titers:

In their response GSK indicates that their investigation into the reagents and history of the study 005 samples used in the retest suggest a combination of factors including multiple ---(b)(4)----- of these samples -----(b)(4)----- for up to (b)(4) years, and the use of a lot of human complement which had exceeded the shelf-life. All factors contributed to the (b)(4) titers.

It is indicated that regardless of the bacterial -----(b)(4)----- or the complement lot used (b)(4), study 005 samples yielded significantly (b)(4) hSBA titers compared to the original testing of the samples. The study results are presented as the ratio of the Geometric Mean (GMR) titers of the retest titers to the original test titers in Table 5.

[(b)(4)]

It is indicated that study 005 samples used in the retest hSBA were from the ---(b)(4)----- because the aliquots prepared for the clinical studies were exhausted. Although the sponsor can not specifically determine how many times study 005 samples underwent –(b)(4)---- they estimate that the -----(b)(4)----- phase of the study prior to their use for the hSBA post-hoc testing. The sponsor also indicates

that the history of the samples used at the time of hSBA-MenY retesting, as well as the exact number of additional ---(b)(4)----- cycles the samples went through after clinical results for Hib-MenCY-TT-005 were finalized, are not exactly known. It is indicated that all samples for the MenY retesting performed in September 2008 most likely came from the ----(b)(4)----- (which had been -----(b)(4)-----). The original validation documents submitted to BLA 125363/0 contained stability data of -----(b)(4)----- . Thus, study 005 samples went through significantly -----(b)(4)----- than what was validated. As a result, the sponsor concluded that the -(b)(4)-- in titers in study 005 samples was most likely due to the age of the samples -----(b)(4)----- and/or to the number of additional ---(b)(4)----- these samples went through prior to the MenY hSBA retesting in September 2008.

In their response, the sponsor provided results of hSBA tests from 31 samples which underwent -----(b)(4)----- . The data showed that the GM titers of all samples analyzed with valid titers after -----(b)(4)----- were all within the acceptable range of ---(b)(4)----- when compared to the reference condition of 1 cycle (Table 6). These results suggest that the sera were stable in hSBA even after ----(b)(4)-----.

[(b)(4)]

The sponsor also provided information about the ----(b)(4)----- . It is indicated that lot (b)(4) was prepared in January 2005. According to the SOP, each hC' shelf-life was set for -(b)(4)----. The retesting of the 005 samples was done in September 2008 and therefore exceeded the (b)(4) shelf-life of (b)(4) lot. The sponsor states that in addition to the age of the samples and/or the number of -(b)(4)---- cycles of the samples, the use of expired complement may have resulted in -(b)(4)--- hSBA titers of study 005 serum samples.

The sponsor's response is not adequate. I would recommend CR Letter Comment #1 below.

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.

Explanations provided for the --(b)(4)-- in retested study 008 samples:

In the original BLA, without presenting data the sponsor had mentioned that, in addition to the study 005 samples, (b)(4) samples from study 008 had also yielded (b)(4) hSBA titers when retested. In the CR letter CBER asked the sponsor to provide the data for the retest of study 008. In their response the sponsor stated that the actual number of samples tested for study 008 was (b)(4) and not (b)(4). The data for the (b)(4) study 008 samples are presented in Appendix 2 of the document "efficacy-hsba-meny". The results of the retesting of study 008 samples are also presented as the GM ratio of retest titer to the original titers as presented in Table 6.

[(b)(4)]

The sponsor indicates that the expired (b)(4) lot was used in (b)(4) tests in which ----(b)(4)---- were used. Both the tests yielded a GMR of 0.27. Table 6 shows that the --(b)(4)-- in GMR with other (b)(4) lots were not as dramatic as the lot (b)(4). However, in their response to CBER question 1b the sponsor provided a table (Table 2) where they presented data for the (b)(4) study 007/008 samples re-tested with the non-expired complement lot --- (b)(4)-- and the (b)(4) lot -(b)(4)--. Although the geomean of the ratio of the re-test titer/ref titer (0.47) for this experiment was higher than the re-tests conducted with the expired -----(b)(4)-----, the re-testing of these samples demonstrated a lower value in the re-test for 11 of the (b)(4) samples. Nine of the (b)(4) retest values are greater than two-fold lower than the reference value. In two cases the retest value is equal to or less than four-fold of the original value. These data do not strongly support the stability of the hSBA for the Men Y over time.

The sponsor also states that the data reported in the Clinical Study Report for Phase II and III testing presented in the BLA were generated using inactivated aliquots specifically prepared for hSBA testing. It is indicated that these samples were tested using validated parameters for human

----(b)(4)----- and went through at least -----(b)(4)----- which is significantly more the validated -----(b)(4)----- . You hypothesize that excessive -----(b)(4)----- may have led to ---(b)(4)--- hSBA titers in the Men Y retest. You then tested this hypothesis by retesting immune sera subjected to -----(b)(4)----- in hSBA. Your results showed that hSBA titers were not affected significantly even after ----(b)(4)----- concluding that the increased -----(b)(4)----- are unlikely to be the sole reason for the -- (b)(4)-- in hSBA titers over time. You have also suggested that the age 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 (b)(4)--. As a result, we believe that the reasons for the -- (b)(4)-- in study 005 hSBA titers remain unknown. Please comment on any additional information you may have that would explain the -- (b)(4)-- in study 005 hSBA results.

2. In your 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 (b)(4) samples. Nine of the (b)(4) retest values are greater than two-fold lower than the reference value. In two cases the retest value is equal to or greater than four-fold lower than the original value. These data do not strongly support the stability of the hSBA for the Men Y over time.

In addition, you provided data relevant to the reliability of the hSBA for Men Y in response to Item 3a. 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). Note that seven out of (b)(4) 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 ---(b)(4)----. The samples with only one replicate provided are not included in the totals. A substantial amount of data is missing from the table precluding complete assessment of assay stability.

The (b)(4) in titer seen in the repeat analyses for samples from Study Hib-MenCY-005, in conjunction with the (b)(4) in titers and the discrepancies in the data submitted in response to Items 1b and 3a, raise concerns over the ability of the hSBA for the Y strain to produce reliable or consistent data over time. While sample storage may have been an issue in the reanalysis of the Hib-MenCY-005 samples, the additional data provided indicate that sample handling may not be the only issue. Of critical importance is the control of the assay during the analysis of the samples from the pivotal studies.

- a. Please provide data that support the stability of the assay for the time frame during which these samples from pivotal studies were analyzed. Data that would be supportive include all control data 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 course of the sample analysis from the pivotal studies should also be included.

- b. Please provide the blinding and randomization scheme for analysis of the samples from the pivotal studies to show that small changes in the assay over time would have affected all groups from a given study equally.
- c. Given the apparent instability of the hSBA for the Y strain, please address the following additional issues:
- (1) Regarding the use of the ----(b)(4)---- algorithm, please provide data that demonstrate that the ----(b)(4)---- algorithm maintains consistent assay performance across changes in control and complement lots. Please show 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.
 - (2) 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 have an R^2 greater than (b)(4).