

**DEPARTMENT OF HEALTH & HUMAN SERVICES**  
FDA, Center for Biologics Evaluation and Research

**MEMORANDUM**

Date: 25 August 2011

From: Tina S. Roecklein, M.S., Consumer Safety Officer, DBPAP, OVRR

Through Jay E. Slater, M.D., Director, DBPAP, OVRR

Subject: Product Review Memo for BLA Supplement 125363/0 (MenHibrix)

Sponsor: GlaxoSmithKline (GSK)

To: File for 125363/0

**Documents Reviewed:**

Amendment 12, dated 15 April 2011 (Response to CR letter issued 11 June 2010)

**Summary/Background:**

On 12 August 2009, GSK submitted a Biologics License Application (BLA) for Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine. Clinical development of this vaccine, which was originally designated Hib-MenCY-TT, was conducted under US IND -(b)(4)-. The development program for Hib-MenCY-TT was granted Fast Track designation on 24 January 2005. Hib-MenCY-TT vaccine is not licensed in any country or region.

The proprietary name is MenHibrix<sup>®</sup>. MenHibrix is a non infectious vaccine that contains *Neisseria meningitidis* serogroup C capsular polysaccharide (PSC), *Neisseria meningitidis* serogroup Y capsular polysaccharide (PSY), and *Haemophilus influenzae* type b capsular polysaccharide (polyribosyl-ribitol-phosphate, PRP), each individually covalently bound to tetanus toxoid. The vaccine formulation is a lyophilized product supplied in a -(b)(4)- monodose glass container -(b)(4)-, stoppered with rubber closures for lyophilization and closed with flip-off caps. 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 *Neisseria meningitidis* serogroups C and Y and *Haemophilus influenzae* type b.

GSK is requesting an expiration dating period of 36 months at 2-8°C. The date of manufacture of the MenHibrix final container vaccine is defined as the start date for filling into final containers. The expiry date of the MenHibrix lots is calculated (day to day) from the date of manufacture.

An eighty-eight item CR letter was issued on 11 June 2010. From my review of the original submission, I noted 30 deficiencies that were included in the CR letter. GSK provided their response to the CR letter on 15 April 2011. This memo summarizes my review of the CR items that were noted as deficiencies during my initial review.

### **Review of Response to CR letter issued 11 June 2010:**

#### **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.**

The date of manufacture for the MenHibrix lyophilized vaccine is defined as the start date of filling into final containers. The expiry date of the MenHibrix lots is calculated (day to day) from the date of manufacture.

The date of manufacture for the GSK Bio saline diluent is defined as the start date of filling of the lots. The expiry date of the GSK Bio saline diluent lots is calculated (day to day) from the date of manufacture.

The information provided adequately addresses the deficiency.

- 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.**

Quality release tests are equivalent to GSK Bio's release specifications for intermediates, active substances, and final product. Tests, test methods, and specification limits are fixed and described in detail in the respective QC Monograph. Tests and limits are registered via the product registration file and changes are submitted to authorities. Tests and limits have direct impact on the product quality/safety/efficacy profile. Test results are documented in the batch summary information (part of the Certificate of Analysis). Lots that fail to meet any quality release test limit are rejected and are not submitted for lot release. In case of an OOS result, a deviation is initiated investigating the root cause and product impact as well as corrective and preventive actions. If an OOS is suspected

to be due to the use of an invalid test procedure, the lot is retested (b)(4) times. If the (b)(4) consecutive retest values are within the set acceptance criteria, the lot is then released with the final QC result being the mean of the (b)(4) valid consecutive retest values. If an OOS is not due to an invalid test procedure, then the lot is rejected. In addition to the specification limits, alert levels are applied for QC release tests. Alert levels constitute a warning which may result in a corrective action. When the alert level is exceeded (out of consistency, OOC), the supervisor verifies the analytical test method parameters/validity criteria. (b)(4) consecutive OOC warnings result in an investigation into root cause.

Quality Decision (QD) tests are used to make a decision on whether or not an in-process material proceeds from one manufacturing step to the next. These tests have defined specifications. Tests, test methods, and specification limits are fixed and described in detail in the respective QC Monograph. Tests and limits are registered via the product registration file and changes are submitted to authorities. If a batch fails to meet the limits set for a quality decision test, the concerned batch will be discarded. In case of an OOS result, a deviation is initiated and investigated as above for the Quality Release tests. For the in-process material to continue in the manufacturing process, the deviation must indicate there is no impact on product quality. Results of these tests are not submitted with the lot release documentation on a batch by batch basis or documented in the batch summary protocol (Certificate of Analysis). In addition to the specification limits, alert levels are applied to QD tests as described above for QC release tests. The same procedure as above is followed when alert levels are exceeded.

Monitoring tests are used to monitor the process consistency and performance. Tests, test methods, and monitoring ranges are described in detail in the company's internal procedures. There are no "acceptance limits" defined for these tests; however, consistency ranges are defined. These tests have no direct impact on the products quality/safety/efficacy profile. Results are not submitted with the lot release documentation. GSK internally defines consistency ranges (alert and action levels). These ranges are reviewed and adapted on a regular basis according to pre-defined rules as documented in the firm's cGMP system. Batches for which an out-of-consistency (OOC) result is found might be subject to an investigation.

The information provided adequately addresses the deficiency. This information will be used below to determine the adequacy in the firm's response of the requests for additional QC Release tests.

**Regarding Hib-TT, MenC-TT, and MenY-TT Drug Substances:**

35. ---b(4)--- -----  
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**11 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. Sucrose Content;**
- b. -(b)(4)-----**
- c. Free Hib polysaccharide content;**
- d. Free MenC Polysaccharide content;**
- e. Free MenY polysaccharide content;**
- f. Free protein; and**
- g. -----(b)(4)-----**

The firm agreed to include the test for sucrose content by -(b)(4)- as a QC release test for MenHibrix final container as of 15 March 2011. The test specification is “between (b)(4) and -(b)(4)- per vial”. The firm also agreed to include the test for -(b)(4)----- as a QC release test for MenHibrix as of 15 March 2011. The test specification is “between (b)(4) and ---(b)(4)---”.

The firm requests to not implement free PS tests on the final container for the following reasons.

- A valid Free PS content method cannot be proposed at the level of final container (lack of specificity, sensitivity, and accuracy).
- Free PS content and -(b)(4)- are assessed for each monovalent conjugate bulk.
- An -----(b)(4)----- that is able to assess the integrity of the conjugates in the final container has been developed. The -(b)(4)- test is used for QC release and also during stability studies of the final container.

The firm has had much conversation with CBER regarding this issue. The firm submitted to the IND and to this response, technical documents explaining their position. The -(b)(4)- test does appear to detect the degradation of conjugates in the final container and to correlate with free PS content measured on monovalent conjugate bulks. The firm has noted that there is -(b)(4)- variability in the -(b)(4)- assay. The firm performed a thorough investigation of the -(b)(4)- variability and has proposed the following.

- Pre-selected batches of the -----(b)(4)----- will be used for release of future MenHibrix final container commercial lots. These same -(b)(4)- are being used for ongoing stability studies (conjugate bulk and final container). Any change in -(b)(4)- batch of -(b)(4)- will be validated based on pre-selection criteria described in the Protocol.

- -----(b)(4)-----  
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After much discussion and review, we concur with the use of the -(b)(4)- assay instead of the Free PS assay for release and stability testing of final container MenHibrix.

The firm's position is that a valid and relevant free TT content method cannot be proposed at the level of final container due to lack of sensitivity and specificity. It should be noted that -(b)(4)- are quantified on the monovalent conjugate bulks. Low values are obtained at release and remain stable over time.

The firm also proposes not to add a QC release test for -----(b)(4)---- content. PS and -(b)(4)- content are performed on PS-TT monovalent conjugate bulks and the TT/PS ratio is calculated. Since the saccharide content is measured on the final container, the firm feels that there is no need to test ----(b)(4)----. We do not concur with this assessment. -----(b)(4)----- should be measured in the final container as a release test.

The firm did not adequately address the deficiency. Suggested comment for a future CR letter or an Information Request:

We do not concur with your proposal to not add -----(b)(4)---- as a QC Release test for Final Container MenHibrix. Please add --(b)(4)-- as a QC Release test.

**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 ten. 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)-- per mg polysaccharide”. However, the batch analysis data show that --(b)(4)- batches have an -(b)(4)- level of less than -(b)(4)- per mg polysaccharide and the remaining batch has an -(b)(4)- level of (b)(4) -- per mg polysaccharide. 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)-- per mg polysaccharide”. However, the batch analysis data show that --(b)(4)- batches have an --(b)(4)-- level of less than -(b)(4)- per mg

**polysaccharide and the remaining -(b)(4)- batches have an -(b)(4)- level of ------(b)(4)----- per mg polysaccharide. Please revise your proposed specification to be reflective of actual validation data.**

- c. In Module 3.2.P.5.1, the ----(b)(4)--- level specification for MenHibrix final product is “not more than --(b)(4)--/dose.” However, the batch analysis data show that the -(b)(4)- levels are always less than -(b)(4)- IU/dose. Please revise your proposed specification to be reflective of actual validation data.**

The firm has taken into account ------(b)(4)----- requirements (------(b)(4)---- and WHO recommendation (TRS 924) in the selection of the specifications for polysaccharide bulks. The specification was calculated based on current data on all *Neisseria meningitidis* polysaccharides (A, C, W, and Y). The “not more than -(b)(4)- per mg PS” was chosen even though most of the data obtained to date are below -(b)(4)- per mg PS. It was noted that this specification is more stringent than the limit proposed by -(b)(4)- and WHO of “less than ------(b)(4)-----”. In addition, to specification limits, there are lower and upper alert limits for ----(b)(4)---

Based on FDA’s “Guideline on validation of -(b)(4)- test as end product -(b)(4)- test for human and animal parenteral drugs, biological product and medical devices”, December 1987, the administration limit for endotoxin is -(b)(4)- body weight/dose by parenteral route. Therefore the acceptance limit of not more than -(b)(4)-/dose complies with the FDA guidance. In addition to the specification, there are lower and upper alert limits.

I conferred with an --(b)(4)-- expert (W. McCormick) on this response. We found the response did not adequately address the deficiency. Suggested comment for a future CR letter or an Information Request:

We note that you calculated the --(b)(4)-- specification based on pooled data from *Neisseria meningitidis* polysaccharides (A, C, W, and Y). However, the calculation of --(b)(4)-- specifications should be serotype specific. Also, please note that the FDA’s “Guideline on validation of -(b)(4)- test as end product -(b)(4) test for human and animal parenteral drugs, biological product and medical devices” dated December 1987 which you reference as a source for acceptance limits has been withdrawn and is no longer an active Guidance document. Therefore this Guidance should not be used or referenced when establishing specifications or acceptance limits. 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.

- 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 Free Hib by -(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)(4)- additional Hib-TT lots were tested for free Hib content by both -(b)(4)- and -(b)(4)- methods. Results were provided and the data shows that the methods are equivalent.

The firm has adequately addressed the deficiency.

- b. **In Module 3.2.S.7.3, you provide stability data for commercial bulk conjugate lots. We note that there is a -(b)(4)- in free polysaccharide C content by -(b)(4)- between your time--(b)(4)- testing and the -(b)(4)- and -(b)(4)- time points. We also note that there is an -(b)(4)- in free polysaccharide Y content by -(b)(4)- between your time--(b)(4)- testing and the ----- (b)(4)----- time points. Please provide an explanation for these results and the variability in your assays.**

This was discussed as a follow-up to Question 66 and is discussed there. The assay variability was not provided as requested.

The firm did not adequately address the deficiency. Suggested comment for a future CR letter or an Information Request:

The variability in your assays was not provided as requested. Please provide the assay variability for your -(b)(4)- assay in comparison to ----- (b)(4)-----.

- 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)-.**



The firm agrees to review the current specification limit for the free PSY content by (b)(4)-. The firm will apply a provisional specification limit of “not more than (b)(4)-”. If the specification needs to be revised (based on results of at least (b)(4)- lots), the firm will provide the data in a post approval supplement.

The firm has adequately addressed the deficiency.

- 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.**

The firm has developed (b)(4) different (b)(4) methods that are used for (b)(4) different tests.

- 1) The -----(b)(4)----- is used to detect free PS in the ----(b)(4)--- of conjugate bulk -----(b)(4)----- . This assay was used for QC release of clinical lots of Men-TT and Hib-TT conjugates. This assay is also a characterization test performed on commercial consistency Men-TT and Hib-TT conjugate bulks. During validation of the method, it was determined that it was not possible to demonstrate accuracy of the method. Therefore, the (b)(4)- was replaced with the chemical methods.
- 2) The ----(b)(4)---- is used as a read-out method for the (b)(4)- test performed as a QC release on the final container. This assay assesses the integrity of the conjugates (----- (b)(4) -----).

----- (b)(4) -----  
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The firm has adequately addressed the deficiency.

- 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.**

The ----(b)(4)---- is not accurate for the detection of small oligosaccharides. This triggered the development of a free PS test with chemical detection. Clinical conjugate lots were retested with Free PS chemical methods. Similar Free PS results were obtained for clinical lots compared to commercial lots.

The -----(b)(4)----- method was used as a QC release test and stability testing of MenHibrix final container clinical lots to assess free Hib, free PSC, and free PSY content. In addition, MenHibrix clinical lots were tested by -----(b)(4)----- at

QC release and during stability. The data provided show that clinical MenHibrix lots are comparable to commercial MenHibrix lots.

Based on this data, the integrity of the clinical lots can be appropriately measured. The firm has adequately addressed the deficiency.

- f. You propose to replace 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.**

Data is provided showing that -----(b)(4)----- is able to detect degradation of the product and that a change in -----(b)(4)----- correlates with a change in Free PS.

The firm has adequately addressed the deficiency.

- g. Please provide stability indicating validation data that demonstrate  
that the -----(b)(4)----- assays can accurately  
quantify the --(b)(4)-- in free polysaccharide due to degradation of  
product.**

Stability indicating validation data for free PS by -----(b)(4)----- were included in the method validation reports in the original submission. I reviewed these validation reports. Another reviewer (R. Gupta) asked specific questions on these validations as part of the CR letter and he is in the process of reviewing their response. I will defer the review of the validation reports to this reviewer.

**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 PSC-PSY 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 PSY content for MenHibrix is not less than (b)(4)- 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.**

The firm agrees to revise the specifications to include an upper limit. Since these tests are performed on final container vials containing -(b)(4)- overage of -(b)(4)----- product, they propose to express the specification in PS content per vial.

- Hib content between ----(b)(4)----- per vial
- Total PSC-PSY content between -----(b)(4)----- per vial
- Total PSY content between -----(b)(4)----- per vial
- Total PSC content between -----(b)(4)----- per vial

The firm has adequately addressed the deficiency.

- 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)-) 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.**

Specifications for saline diluent manufactured at -(b)(4) or GSK are identical and comply with b(4) requirements. Therefore, diluents from either manufacturer, once approved, will be -----(b)(4)----- to reconstitute product for future release testing.

The firm has adequately addressed the deficiency.

**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) for the formulated bulk. 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.**

(b)(4) additional formulated bulks were manufactured to validate the proposed (b)(4) hold time. QC release data on final container lots manufactured from the formulated bulk lots stored for -----(b)(4)----- meet release specifications.

The firm has adequately addressed the deficiency.

**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.**

The firm proposes to use -(b)(4)- instead of Free PS assays. This is discussed in detail in Question 67 (Release testing). I concur with the firm's proposal.

The firm has adequately addressed the deficiency.

- 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 -(b)(4)- time point.**

The firm states that polysaccharide content would not add any value to the stability program and therefore proposes not to add. We do not concur with this proposal. The PS content during stability provides a baseline in case there is a change in -(b)(4)-.

The firm did not adequately address the deficiency. Suggested comment for a future CR letter or an Information Request:

We do not concur with your proposal to not assess polysaccharide content (Hib, MenC, and MenY) during stability. Please revise your protocol for future on-going stability studies to include assays to assess polysaccharide content (Hib, MenC, and MenY) at -(b)(4)- time point.

- c. Your specification for ----(b)(4)--- content is listed as not more than --(b)(4)--/dose. 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 (b)(4) point.**

The protocol for future on-going stability includes sterility testing by -----(b)(4)----- at Time -----(b)(4)----- . In addition, container closure is tested at -(b)(4)-. Therefore,

the firm does not feel ---(b)(4)-- testing is needed during routine stability. I concur with this. Therefore, this makes discussion on the specification a non-issue.

The firm has adequately addressed the deficiency.

- 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 ----(b)(4)----. 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 b(4) diluents manufactured by GSK and by -(b)(4)-.**

Stability data in support of reconstituted drug product include (b)(4) evaluation. All values, including (b)(4) values remain in specification. The firm proposes to use (b)(4) instead of Free PS assays. This is discussed in detail in Question 67 (Release testing). I concur with the firm's proposal. The -(b)(4)- results remain in specification.

The firm commits to perform on-going annual stability studies on reconstituted drug product. The stability protocol has been updated to include the -(b)(4)- holding time of the reconstituted vaccine. Description, ---(b)(4)--- will be performed on the vaccine reconstituted with saline diluent and after -----(b)(4)----- . The lyophilized product will also be tested for -----(b)(4)----- . The integrity of the container closure is evaluated at the end of the product shelf-life. The reconstituted vaccine will also be tested for volume.

Specifications for the saline diluents are identical for -(b)(4)- and GSK and comply with b(4) requirements. Therefore, diluents from either approved manufacturer will be used in an -----(b)(4)----- way to reconstitute drug product. -(b)(4)- diluents should be represented in stability if planning to use both for commercial distribution for the US. This should be formalized in the protocol.

The firm did not adequately address the deficiency. Suggested comment for a future CR letter or an Information Request:

Please provide written procedures to ensure that all licensed, commercially distributed diluents are represented during reconstitution during MenHibrix stability testing.

- 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 (b)(4)**

**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.**

The firm submitted updated stability data. -(b)(4)- commercial consistency lots (------(b)(4)-----) that previously only had -(b)(4)- months of real time data now have acceptable results up to --(b)(4)--. An additional commercial lot (-----(b)(4)----) that was prepared after the formulated bulk was stored for -----(b)(4)---- °C that previously only had (b)(4) months of real time data now have acceptable results up to --(b)(4)--.

The firm proposes a 36 month expiry dating on final filled drug product. Their rationale is the equivalency of clinical consistency and commercial consistency lots. The firm has 36 months of stability data on clinical consistency lots that meet acceptance results. We do not concur with this proposal. There are significant manufacturing changes between the clinical development lots and the commercial consistency lots such that the data from the clinical lots are not fully supportive of their proposed expiration dating for commercial product.

- Different filling/lyophilization batch size
- Different lyophilization process
- Multiple changes in buildings (Hib, TT)

The expiration dating should be based on real-time stability accrued for your commercial stability lots. The firm did not adequately address the deficiency. Suggested comment for a future CR letter or an Information Request:

We do not concur with a 36 month shelf life for MenHibrix as proposed in the BLA. Please revise the expiration data to reflect the real time stability data (i.e., --(b)(4)--).

**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.**

The firm agreed to place -(b)(4)- lot of Purified Hib-TT Bulk Conjugate, Purified Meningococcal Group C Conjugate Bulk, and Purified Meningococcal Group Y Conjugate Bulk each year on stability. Stability protocols were submitted to the file. The Hib-TT, MenC-TT, and MenY-TT lots included in the annual stability studies will not be used in the manufacture of the MenHibrix b(4) lot placed on commercial stability. The

firm does not propose to test sterility for Hib-TT, MenC-TT, or MenY-TT or --(b)(4)-- for MenC-TT or MenY-TT.

The firm does not propose to place the polysaccharide purified bulks on annual stability. Their rationale is that these bulks are in -----(b)(4)----- and stored at -(b)(4)- and were shown to be stable when stored under these conditions.

The firm did not adequately address the deficiency. Suggested comment for a future CR letter or an Information Request:

Please add sterility testing to the annual stability protocol of Hib-TT. Please add sterility and --(b)(4)-- testing to the annual stability protocol of MenC-TT and MenY-TT.

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.

- 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: -----(b)(4)----- have been deleted from the protocol. Please provide a justification for these proposed changes.**

The firm does not consider -----(b)(4)----- identity tests as informative for stability of the product. -----(b)(4)----- tests are not considered of any added value to evaluate stability of the product since a regular (yearly) sterility test is in place together with a container closure integrity test at the end of shelf-life. I concur.

The firm has adequately addressed the deficiency.

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

The firm submitted updated stability tables. The firm provided complete stability data for -(b)(4)- saline diluent lots manufactured using the current process but with the previous ----- ((b)(4)). Complete stability data show that all lots comply with the specifications thereby supporting the shelf-life of ----(b)(4)----- for diluent -b(4)----- . The firm

also provided updated stability data for -(b)(4)- diluent lots manufactured with the current process and using the new -(b)(4)----- . Current available data show that the -(b)(4)- lots comply with the specifications up to -----(b)(4)-----.

The firm requests a shelf-life of --(b)(4)-- when stored at --(b)(4)-- for diluent in -b(4)----  
----- I concur with this since the firm provided --(b)(4)-- data using the current process. A change in -b(4)--- post-approval does not normally require a change to the expiration dating.

The firm has adequately addressed the deficiency.

**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.**

The -(b)(4)- batches provided in the BLA were produced from the same bulk (--(b)(4)--). Additional data on (b)(4) diluent lots (representing (b)(4) different bulk lots) were provided in the response. These lots are prepared with the current process and the current -b(4)---. All lots comply with the specifications.

The firm has adequately addressed the deficiency.

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

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



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

- -----(b)(4)----- independent sessions)
- All valid
- Comparability of new and old --- (b)(4)---

I reviewed the CPs in detail and also consulted with a DPQ reviewer (R. Gupta) to assess the CPs adequacy. The firm did not adequately address the deficiency. Suggested comment for a future CR letter or an Information Request:

Please address the following deficiencies noted during the review of your Comparability Protocols (CPs) for changes in reference standards.

- a. Most of the CPs have acceptance criteria as differences of less than -(b)(4)- in results generated with new and old reference standards. The CPs for the Free TT and Identity assays contain qualification criteria that comparability between the old and new standard is demonstrated if the results are -(b)(4)-. This approach does not calibrate the new standard against the existing standard and sometimes -(b)(4)- differences can cause problems, particularly when qualifying the reference standard repeatedly and the difference is sequential in one direction. Please develop a primary reference standard for each assay. Please calibrate against the primary reference standard each time a reference standard is changed.
- b. The number of qualification runs varies depending on the assay. Please run a minimum of -(b)(4)- qualification runs.
- c. The amount of samples (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.
- d. Some of the CPs contain acceptance criteria for assay validity and some do not. Please include assay acceptance/validity criteria as part of the CP. Please include in the qualification criteria that both old and new standard must meet assay acceptance/validity criteria.
- e. The CP for -----(b)(4)----- for Hib-TT in conjugate bulks and MenHibrix b(4) state that the reference is final container Hib. Please confirm that this is Hiberix.

83. **The package insert states that MenHibrix should be administered within -(b)(4)- of reconstitution. 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.**

The firm agreed to remove the statement regarding “storage at controlled room temperature between 2 and -(b)(4)-” from the package insert and replace it with the following:

“MenHibrix should be administered within -(b)(4)- of reconstitution. After reconstitution, store refrigerated between 2 and 8 °C (36 and 46 °F). Discard the reconstituted vaccine if not used ----- (b)(4) ----- . Do not freeze. Discard if the vaccine has been frozen.”

The firm provided the updated package insert and I confirmed that the changes have been made. The firm has adequate stability data to support the revised statement.

The firm has adequately addressed the deficiency.

**Comments in my original memo dated 4 May 2010 that did not go into the CR letter dated 11 June 2010:**

3. In Section 3.2.A.2, you state that ----- (b)(4) -----, which is an ingredient in ----- (b)(4) -----, can be derived from animals originating from --- (b)(4) ----- . ----- This medium is used for the manufacture of ----- (b)(4) ----- . In addition, this medium is used for ----- (b)(4) ----- and ----- (b)(4) ----- is not currently on the USDA’s list of acceptable countries for the use of animal sourced components. Please provide detailed information on using an alternate source supplier for this ingredient, and indicate how you plan to replace the ----- (b)(4) ----- using components from acceptable countries.

It was determined after this was written in the memo that the b(4) Guidelines do not pertain to milk products so therefore ----- (b)(4) ----- from -- (b)(4) -- is acceptable.

15. In Section 3.2.S.7 (Stability) you provide stability data in support of the hold time for the MenC-TT and MenY-TT conjugate bulks. You propose a shelf life of -(b)(4)- based on clinical lots and data for an EU approved product. However, multiple manufacturing process changes have been made between the clinical lots and the commercial lots and are not fully supportive of your proposed -(b)(4)- expiration date. Please provide stability data for the final -(b)(4)- time-point for the conjugate bulks. In addition, we have the following comments regarding stability of your conjugate bulks:

- d. An extension in expiration dating to -- (b)(4) -- would require submission of a Prior Approval Supplement. Please acknowledge.

1 Page determined to be not releasable: b(4)

---b(4)---  
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Regarding Drug Product Specifications and QC Release:

8. We do not concur with your proposal to not add ---b(4)--- as a QC Release test for Final Container MenHibrix. Please add ---b(4)--- as a QC Release test.

9. We note that you calculated the ---b(4)--- specification based on pooled data from *Neisseria meningitidis* polysaccharides (A, C, W, and Y). However, the calculation of ---b(4)--- specifications should be serotype specific. Also, please note that the FDA's "Guideline on validation of -(b)(4)- as end product ---b(4)--- test for human and animal parenteral drugs, biological product and medical devices" dated December 1987 which you reference as a source of acceptance limits has been withdrawn and is no longer an active Guidance document. Therefore this Guidance should not be used or referenced when establishing specifications or acceptance limits. 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:

10. We do not concur with your proposal to not assess polysaccharide content (Hib, MenC, and MenY) during stability. Please revise your protocol for future on-going stability studies to include assays to assess polysaccharide content (Hib, MenC, and MenY) at each time point.

11. Please provide written procedures to ensure that all licensed, commercially distributed diluents are represented during reconstitution during MenHibrix stability testing.

12. We do not concur with a -(b)(4)- shelf life for MenHibrix as proposed in the BLA. Please revise the expiration data to reflect the real time stability data (i.e., -(b)(4)-).

13. Please add sterility testing to the annual stability protocol of Hib-TT. Please add sterility and -(b)(4)- testing to the annual stability protocol of MenC-TT and MenY-TT.

14. 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.

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

15. Please address the following deficiencies noted during the review of your Comparability Protocols (CPs) for changes in reference standards.

- a. Most of the CPs have acceptance criteria as differences of less than -(b)(4)- in results generated with new and old reference standards. The CPs for the Free TT and Identity assays contain qualification criteria that comparability between the old and new standard is demonstrated if the results are -(b)(4)-. This approach does not calibrate the new standard against the existing standard and sometimes -(b)(4)- differences can cause problems, particularly when qualifying the reference standard repeatedly and the difference is sequential in one direction. Please develop a primary reference standard for each assay. Please calibrate against the primary reference standard each time a reference standard is changed.
- b. The number of qualification runs varies depending on the assay. Please run a minimum of -(b)(4)- qualification runs.
- c. The amount of samples (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.
- d. Some of the CPs contain acceptance criteria for assay validity and some do not. Please include assay acceptance/validity criteria as part of the CP. Please include in the qualification criteria that both old and new standard must meet assay acceptance/validity criteria.
- e. The CP for -----(b)(4)----- for Hib-TT in conjugate bulks and MenHibrix FC state that the reference is final container Hib. Please confirm that this is Hiberix.

**PMCs:**

The firm provided the following PMCs in their response dated 15 April 2011.

------(b)(4)-----  
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The firm commits to provide validation data on the -(b)(4)- content test on the -----(b)(4)----- TT by 4<sup>th</sup> Quarter 2011.

**Recommendation:**

Based on review of the file, I do not recommend approval at this time based on the above list of deficiencies.