

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

MEMORANDUM

Date: 12 June 2012

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:

Original Submission, dated 12 August 2009 (PI, Labeling, and Lot Release Protocol)

Amendment 21, dated 30 November 2011 (Response to CR letter issued 21 September 2011)

Amendment 24, dated 30 January 2012 (Response to CR letter issued 21 September 2011)

Amendment 27, dated 4 April 2012 (Response to IR sent 20 March 2012)

Amendment 28, dated 13 April 2012 (Updated PI and Labeling)

Amendment 29, dated 20 April 2012 (Response to IR sent 20 March 2012)

Amendment 30, dated 2 May 2012 (Additional information on PS Content Assays and Stability)

Amendment 31, dated 9 May 2012 (Response to IR sent 2 May 2012 and Revised LRP)

Amendment 32, dated 16 May 2012 (Response to IR discussed on 14 May 2012, LRP and History Table for Specification Revisions)

Amendment 34, dated 25 May 2012 (Response to IR discussed on 23 May 2012, LRP and History Table for Specification Revisions)

Amendment 35, dated 4 June 2012 (Response to IR discussed on 23 May 2012 and IR emailed on 29 May 2012(K. Prutzman to N. Pyle and J. Gould): Lot Number – Expiry assignment and PMCs)

Amendment 36, dated 12 June 2012 (Response to IR discussed on 8 June 2012 and 11 June 2012: PMCs and Clarification on Location of Labeling and Packaging)

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[®]. 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 original submission proposes that the vaccine is to be reconstituted prior to intramuscular injection, with a liquid saline diluent supplied in ---(b)(4)----- containing (b)(4) mL of diluent. As part of this response, the GSK proposes to withdraw the 0.9% sodium chloride diluent (b)(4)-presentation from the BLA and replace it with a 0.9% sodium chloride diluent vial presentation manufactured by -----(b)(4)----- . The diluent vial presentation allows for reconstitution with a measured volume of 0.6 mL (the diluent vial contains an excess fill volume targeted at 0.85 mL), and subsequent administration of the 0.5 mL dose. 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. A second twenty-six item CR was issued on 21 September 2011. From my review of the response dated 15 April 2011, I noted 15 deficiencies that were include in the second CR letter. GSK provided their response to the second CR letter on 30 November 2011 and 30 January 2012. This memo summarizes my review of the CR items that were noted as deficiencies during my review of GSK's response to the second CR letter.

Changes Submitted as part of Amendment 21 dated 30 November 2011:

1. GSK proposes to withdraw the 0.9% sodium chloride diluent -(b)(4)- presentation from the BLA and replace it with a 0.9% sodium chloride diluent vial presentation manufactured by -----(b)(4)----- . This same change is being reviewed for ---b(4)----- . I defer the review of this presentation to other team members.
2. GSK proposes to introduce the --(b)(4)- facility for packaging operations. One 10 pack carton of lyophilized vaccine (packaged at GSK Bio --(b)(4)-) and one 10 pack carton of sodium chloride diluent (packaged at -----(b)(4)----- are combined into an outer box via a kitting process that will be performed at GSK Bio --(b)(4)- . This site was approved for packaging of Engerix-B on 7 August 2009. Additional products introduced into this facility will be reported in the Annual Report. The addition of MenHibrix is being reported as part of this BLA. I defer the review of this additional facility to the Facility reviewers.
3. GSK proposes to remove the monitoring test for --(b)(4)--- content at the first --(b)(4)--- during manufacture of MenY polysaccharide. GSK recently became aware that the presence of --(b)(4)--- in the sample matrix interferes with the test for --(b)(4)---content. GSK has no alternative method for testing --(b)(4)--- content at the ----(b)(4)----- . --(b)(4)--- content is performed as a QC release test on the final MenY polysaccharide (b)(4) and on MenHibrix final container vaccine. This change is consistent is what is being performed for the manufacture of MenC polysaccharide and Hib polysaccharide. Monograph number 200319 (Monitoring Tests for MenY Bulk) has been revised. I concur with the information provided to support this change.
4. In the 15 April 2011 response to the first CR letter, GSK proposed providing certain validation data as PMCs. The validation data is provided in this submission. The majority of these PMCs were requested by DBSQC and I will defer the review to them.
 - a. Item 39a: -----(b)(4)----- will be a QC release test with a provisional limit of “not more than -----(b)(4)----- . This specification limit will be reviewed once at least (b)(4) lots of -----(b)(4)--- MenY polysaccharide are produced and tested for -----

--(b)(4)----- . This PMC is ongoing and will be part of MenHibrix final approval.

- b. Item 39a: Asymmetry by (b)(4) will be assessed during the stability on ----(b)(4)----- MenY lots to validate -----(b)(4)----- for which results will be reported by 4Q2011 as a PMC. This PMC has been resolved as part of the response to CR Item 13. See below for additional information.
- c. Item 40b: GSK proposes to provide the validation data on the --(b)(4)- ----- test on the -----(b)(4)----- TT as a PMC by 4Q2011. This was provided and reviewed by E. Keller. This PMC has been resolved during this review cycle.
- d. Item 63: The company commits to repeat the stability study on ----(b)(4)----- MenY lots with the addition of the (b)(4) and ---(b)(4)--- tests. The company commits to provide stability results on ----(b)(4)----- MenY by 4Q2011 as a PMC. This PMC has been resolved as part of the response to CR Item 13. See below for additional information.
- e. Item 76: The company commits to provide 36 month data on lots -----(b)(4)----- when available (1Q2012). This PMC has been resolved as part of the response to CR Item 19. See below for additional information.
- f. The remaining PMCs (Items 42, 43, 44, 45, and 49) will be reviewed by DBSQC.

Change in diluent manufacture and packaging location submitted in Amendment 21 dated 30 November 2011

Amendment 21 dated 30 November 2011 includes the introduction of a 0.9% NaCl diluent vial presentation manufactured by -----(b)(4)----- . This presentation will allow for a measured volume (0.5 mL) for administration using a syringe supplied by the Health Care Provider. The amendment provides a letter of authorization to allow GSK to reference -----(b)(4)----- in support of the change. The (b)(4) was originally reviewed in support of the identical change to GSK's product Hiberix (STN 125347/(b)(4)).

This amendment also allows for the GSK ---(b)(4)----- facility to perform final packaging: one 10 pack carton of lyophilized vaccine packaged at the --(b)(4)- site and one 10 pack carton of diluent packaged at (b)(4) are combined into an outer box via a kitting process performed at the --(b)(4)-- facility. This facility was approved for

labeling/packaging August 2009 under STN -----(b)(4)-----
-----.

MenHibrix is a lyophilized vaccine to be reconstituted with supplied diluent at time of use. The amendment contains the following.

- manufacture -----(b)(4)-----
----- of the 0.9% NaCl diluent by -----(b)(4)-----
used for reconstitution of the lyophilized MenHibrix vaccine
- labeling and primary packaging of the lyophilized MenHibrix vaccine at the GSK facility in -----(b)(4)-----
- final labeling and packaging (kitting) of MenHibrix vaccine with the packaged diluent into one combination package, also at the facility in -----(b)(4)-----

GSK provided the following in support of these changes.

- Letters of Authorization to reference -----(b)(4)----- and to reference container-closure Drug Master Files
- Modules 2 and 3 of the eCTD sections to include
 - o CMC information extracted from -----(b)(4)-----, including (b)(4) months real time and accelerated stability data on (b)(4) process validation batches, and release data on a (b)(4) process validation batch.
 - o Facility information relating to the new diluent vial presentation for both (b)(4) and for the --(b)(4)-- facility
- Module 3.2.P.3.1 Manufacturer – MenHibrix and Module 3.2.P.3.3 Description of Manufacturing Process and Process Controls – MenHibrix which have been updated to incorporate the packaging operation being performed at the --b(4)---- facility.

The product is a compendial diluent of 0.9% NaCl in -----b(4)----- and meets --(b)(4) and the --b(4)- monograph for NaCl injection for physicochemical and biological properties which is used to reconstitute the lyophilized MenHibrix product. It is filled into -----(b)(4)---- treated glass vials closed with an elastomeric stopper, and sealed with ---(b)(4)--- over seal. The target fill volume/vial is 0.85 mL to ensure 0.6 mL for reconstitution. Release testing is performed by (b)(4) and final release is performed by GSK -(b)(4), Belgium. The -(b)(4) site performs the container closure integrity test (CCIT, approved STN 125347/(b)(4)). The date of manufacture of the diluent is defined as the start date for filling into final containers.

Stability is conducted at both -----(b)(4)----- at GSK. The submission provides three months stability for validation lots -----(b)(4)-----
----- . The 3 month data provided includes visual appearance, -----(b)(4)-----
-, sodium chloride assay, -----(b)(4)-----, sterility, and container closure integrity. Accelerated stability for lot -----(b)(4)----- is also provided. GSK plans to place a minimum of (b)(4) commercial lot on long term stability

each year, if manufactured. At this point, GSK provided (b)(4) months of acceptable stability data. CBER has agreed to approve a 24 month expiry date for diluent when stored at 2-25 °C. Extension of expiry dating to (b)(4) will be submitted as a future PAS.

Reviews on the manufacture of diluent including the facilities and equipment were performed by other reviewers. The reviews can be found in the EDR as part of the following files.

- MenHibrix (125363/0)
- Hiberix (125347/(b)(4))
- DMF for 0.9% NaCl manufactured by ----(b)(4)-----

It was noted during the review that there was a discrepancy between the information provided in the BLA and what was discussed in a telephone conversation on 14 May 2012 and in an email on 15 May 2012 (N. Pyle to J. Temenak).

- The BLA states that labeling and primary packaging of MenHiberix can occur at either GSK (b)(4) (Belgium) or GSK ----(b)(4)-----.
- The telephone/email communication states that the vaccine vials that come from Belgium are received in --(b)(4)- as unlabeled vials. --(b)(4)- performs all labeling and packaging for the vaccine.

CBER contacted the firm on 8 June 2012 to clarify the location(s) that are being requested for primary labeling and packaging of MenHibrix based on the above discrepancy. It was stated to the firm that if primary labeling is being performed in Belgium, then an explanation on the assignment of lot numbers would need to be presented. The concern is that the kitted lot number (assigned in --(b)(4)-) is being used on the label of the vaccine. The labeling in Belgium using a lot number assigned in --(b)(4)- which depends on the availability of diluent in --(b)(4)- is error prone. An explanation of how this potential error will be decreased will need to be presented. More information is provided below in the section Package Insert and Carton Labeling relating to the assignment of lot numbers and expiry dating.

The firm responded via email on 11 June 2012 (J. Gould to J. Temenak, K. Prutzman, and D. Staten). CBER and GSK discussed this response on 11 June 2012. The firm would like to use GSK --(b)(4)- as the primary location for the primary labeling and packaging of vaccine. The firm would like to also request approval of GSK --(b)(4)- (Belgium) as an alternate location for primary labeling and packaging of vaccine. If this alternate pathway was performed, diluent would be shipped from -----(b)(4)----- to GSK (b)(4) (Belgium). The kitting of vaccine and diluent would also occur in --(b)(4)- (Belgium). Therefore, the error would be reduced by having this all occur in the same location. GSK has one SAP system that is used by all GSK locations. This would eliminate the possibility that the same lot number would be assigned on product by both -----(b)(4)-----. It was explained in the teleconference that this alternate pathway was not clearly explained in the submission. I asked if the firm had shipping validation data for the diluent to be shipped from -----(b)(4)----- to

-(b)(4)-, Belgium. The firm responded that this was not provided. At the end of the teleconference, the firm agreed to withdraw the request for the alternate pathway of primary packaging and labeling of vaccine as well as kitting of vaccine/diluent to be performed at -(b)(4)- (Belgium) since the submission of shipping validation data would delay BLA approval. This alternate pathway will be submitted as a post approval supplement.

Amendment 36 was submitted on 12 June 2012. This amendment clarifies the locations of manufacture and specifically withdraws the request to perform primary labeling and packaging of vaccine as well as kitting of the vaccine/diluent at -(b)(4)-. The following is a summary of the locations of manufacture to be approved for MenHibrix.

- Hib, MenC, MenY manufacture at -(b)(4)- (Belgium)
- TT manufacture at -(b)(4)-
- -(b)(4)- Purified TT manufacture at Rixensart (Belgium)
- ---(b)(4)--- and Conjugation (Hib-TT, MenC-TT, MenY-TT manufacture) at Rixensart (Belgium)
- ----(b)(4)---- of MenHibrix at Rixensart (Belgium)
- -(b)(4)- and Lyophilization at -(b)(4)- (Belgium)
- QC Testing at -(b)(4)- (Belgium)
- 100% Visual Inspection at -(b)(4)- (Belgium) or -----(b)(4)-----
- Primary labeling and packaging of MenHibrix at -----(b)(4)-----

- Diluent manufacture -----
------(b)(4)-----

- Kitting of MenHibrix and Diluent at -----(b)(4)-----.

Amendment 36 clarifies the locations for manufacture of MenHibrix. The removal of -(b)(4)- as an alternate location for vaccine primary labeling and packaging as well as kitting of vaccine and diluent, provides assurance of reducing potential error. Shipping validation was not originally provided for the shipment of diluent from ----(b)(4)---- to Belgium. The shipping validation for the transfer of diluent from ----(b)(4)----- was provided and reviewed by S. Byrd.

Therefore, based on the information provided and the CMC and Facility reviews in the EDR, I recommend approval of the (b)(4) 0.9% NaCl diluent to be used for reconstitution of MenHibrix. I concur with a 24 month expiry of diluent when stored at 2-25 °C. Diluent will be shipped from -----(b)(4)----- to GSK ----(b)(4)----- for co-packaging with MenHibrix.

Review of Response to CR letter issued 21 September 2011:

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 has 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 (b)(4). Such a large variability in the calibration of new standards is not acceptable. Please revise the criteria for calibrating new standards for Free TT 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 contains 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.

(b)(4) CPs were provided in the BLA. GSK proposes to remove the following (b)(4) CPs:

- ----(b)(4)----- assay for Free MenC PS content on MenC-TT conjugates
- ----(b)(4)----- assay for Free MenY PS content on MenY-TT conjugates
- (b)(4) assays for determination of MenC and MenY polysaccharide content in MenHibrix by -----(b)(4)-----
- Determination of ---(b)(4)--- in Hib-TT conjugate bulk
- Determination of -----(b)(4)----- in Hib-TT conjugate bulk

- Determination of -----(b)(4)----- in MenC-TT and MenY-TT conjugate bulks
- Identity test by (b)(4) for MenC-TT and MenY-TT in conjugate bulks and in MenHibrix FC
- Identity test by (b)(4) for Hib-TT in conjugate bulks and in MenHibrix FC

GSK updated CP 9000006115CPR001 ((b)(4) assays for determination of the Hib polysaccharide content in MenHibrix by (b)(4)). Resolution of the concerns in Item 4 (a, b, c, d, and e) have been addressed in the updated CP.

In addition, GSK submitted a validation report 9000001118RVR006 providing data related to the change in reference material for the “Hib Identity by (b)(4) on conjugated Bulks (PS-TT) and final container HibMenCY”. The current stock of Batch -----(b)(4)----- is running low. Final container Hib (Hiberix) (b)(4) dose batch -----(b)(4)----- was selected as the standard. This batch conforms to QC release specifications. The data qualifying this new standard is in the provided validation report. The validation of the new standard addresses all the concerns stated above.

The firm is keeping the one CP and providing the validation report for the one assay because of the current stock of reference standards is low and the implementation of new reference standards is required in a short period of time.

Regarding Item 4f, GSK confirmed that the reference for Identity by (b)(4) for Hib-TT conjugate bulks and MenHibrix final container referred to as Hib is final container Hiberix.

I reviewed the above CP for Determination of Hib polysaccharide content in MenHibrix by (b)(4) . I reviewed the validation report provide for the qualification of the new reference standard batch -----(b)(4)----- used for Hib Identity by (b)(4) on conjugated Hib-TT and final container MenHibrix. In addition, I asked Tsai-Lien Lin, Rajesh Gupta, and Freyja Lynn for a consult review.

Based on the review of all submitted information, the firm has adequately addressed my concerns.

5. The CPs provided in response to Item 35 for the ----(b)(4)---- of *Clostridium tetani* ---(b)(4)---- and Hib ---(b)(4)---- are inadequate for the purposes of reporting such changes in your Annual Report. Please provide details for the manufacture of the ---(b)(4)---- . Please note that the CPs should be stand alone documents that do not reference procedures described in the BLA. Also, as above, CPs should have pre-defined acceptance criteria for all tests.

GSK withdrew the submitted CPs for Clostridium tetani and Hib ---(b)(4)---- from the BLA. The firm will submit any new ---(b)(4)---- as a PAS or will submit amended CPs as PAS after approval of MenHibrix.

Based on the review of all submitted information, the firm has adequately addressed my concerns.

6. You provide the in-process quality decision and monitoring tests for each step of the TT purification and ---(b)(4)---- process performed at Rixensart (Table 1 in your response to Item 25). We do not concur with the -----(b)(4)----- TT by (b)(4) testing performed at the first step -(b)(4)-- as a ---(b)(4)----- . While we acknowledge that TT monitoring testing performed during ---(b)(4)--- manufacturing steps is essential to maintain process consistency, CBER also believes that establishing a predefined specification in the ----(b)(4)----- of the purified TT bulks immediately prior to ----(b)(4)----- is equally important in maintaining process consistency. We note that stability studies with the TT bulks clearly indicate that ---(b)(4)-- TT significantly -(b)(4)-- over time. Please establish specifications for the TT -(b)(4)- content at the step -(b)(4)-- just prior to the -----(b)(4)----- of TT that occurs at Rixensart. Also, please revise this test to a quality decision test rather than a monitoring test.

GSK agreed to revise the -----(b)(4)----- testing performed at the (b)(4)--- -----of the Hib-TT and MenC/Y-TT processes from a monitoring test to a quality decision test. The testing is performed just prior to -----(b)(4)----- performed in Belgium. The statistical approach used to calculate the specifications is based on process performance indices. Based on statistical evaluation, the proposed specification is “not less than (b)(4) of the total surface as ---(b)(4)---- TT” for the -----(b)(4)----- at the --(b)(4)--- of Hib-TT and MenC/Y-TT processes. I reviewed the information submitted and asked Freyja Lynn and Tsai-Lien Lin for a consult review to evaluate the statistics involved in setting the specifications. The validation of the method was submitted and reviewed by Michael Schmitt.

Based on the review of all submitted information, the firm has adequately addressed my concerns.

8. Please provide data for the amounts of residual -----(b)(4)-----, and any other byproduct from the conjugation reaction for MenC-TT and MenY-TT in final product.

GSK provided data to show the clearance of all potential residual by products and solvent from the MenC-TT and MenY-TT conjugation reaction in MenC-TT and MenY-TT conjugate bulks.

- a. -----(b)(4)----- Test on Purified Tetanus Toxoid manufactured and released at -(b)(4)-.

GSK agreed to implement the above test as QC release test. The firm validated the percent monomer test on Purified Tetanus Toxoid manufactured and released at -(b)(4)-. The validation report was provided and reviewed by James Keller. -(b)(4) data on the last (b)(4) commercial production lots have been provided. The statistical approach used to calculate the -----(b)(4)----- specification is based on process performance indices. Based on the capability analysis, the firm proposes a release specification of “not less than (b)(4) of the total surface as ---(b)(4)--- TT” to be applied for the release of the Purified TT bulks.

I asked both Freyja Lynn and Tsai-Lien Lin to perform a consult review of the statistical approach of setting this specification.

Based on the initial review by all, it was determined that the specification is appropriately set. However, on further review of Item 12 below, more discussion on the specification was needed with the firm. The expiry of the Purified Bulk is of a concern in Item 12. It was noted that if the release specification was set higher, then the stability of Purified TT bulk could be ensured as it is proven ---(b)(4)--- decreases over time. The resolution of Item 12 results in a specification of not less than (b)(4) for purified TT bulk manufactured at -(b)(4)-. See Item 12 below for more discussion on this matter.

Based on the review of all submitted information, the firm has adequately addressed my concerns.

- b. -----(b)(4)----- MenY polysaccharide.

GSK agreed to implement the above test as a QC release test. The firm validated the -----(b)(4)----- MenY polysaccharide. The validation report was provided and reviewed by Daron Freedberg. The statistical approach used to calculate the -----(b)(4)----- specification is based on process performance indices. Based on the capability analysis, the firm proposes a release specification of --(b)(4)---. I asked both Freyja Lynn and Tsai-Lien Lin to perform a consult review of the statistical approach of setting this specification.

Based on the review of all submitted information, the firm has adequately addressed my concerns.

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

--(b)(4)---. In addition, please provide a specification for the test -----
------(b)(4)-----.

GSK provided a stability update ---(b)(4)--- of storage at (b)(4) for the Purified TT –b(4)- consistency lots. The -----(b)(4)----- was performed as a ----(b)(4)----- . As requested in Item 11a, this assay will be implemented as a QC Release test for future production of TT. The proposed specification for release of Purified TT is “not less than (b)(4) of the total surface as ---(b)(4)--- TT” as discussed in Item 11a. The proposed specification for stability of Purified TT is “not less than (b)(4) of the total surface as ---(b)(4)--- TT”. The proposed stability specification was determined by evaluating the stability profile of (b)(4) purified tetanus toxoid lots. Based on the release specification of NLT (b)(4) and taking into account the loss rate and the associated uncertainties, a stability specification of NLT (b)(4) is proposed. The stability data provided for the Purified (b)(4) consistency lots meet acceptance criteria when a stability specification of NLT (b)(4) is used for –(b)(4)---. GSK proposes a ---(b)(4)--- shelf-life for Purified TT when stored at (b)(4).

Based on review of the submitted information, the following information was sent to GSK on 20 March 2012:

You propose a -----(b)(4)----- release specification of not less than (b)(4) for Purified TT manufactured at -(b)(4)-. You also propose a -----(b)(4)----- release specification of not less than (b)(4) for Purified TT measured directly before ----(b)(4)----- in Belgium. In your response to Question 12, you propose a ----(b)(4)----- stability specification of not less than (b)(4) for Purified TT manufactured at (b)(4) .

- a. Please revise your stability specification to not less than (b)(4) so that it is in line with the specification needed to be used for further manufacture.
- b. You propose a -(b)(4)--- expiration date on Purified TT based on a ----(b)(4)--- stability specification of not less than (b)(4) . Using a stability specification for ----(b)(4)----- of not less than (b)(4) , you only have data to support an expiration date of -(b)(4)--- . Please revise your expiration date to -(b)(4)--- .
- c. The ----(b)(4)----- results for Purified TT are known to decrease over time. To ensure that a ----(b)(4)----- result of not less than (b)(4) is obtained at the end of expiry, the -----(b)(4)----- content at release should be closer to not less than (b)(4) . Please comment.

The firm responded to this information request in Amendment 29 dated 20 April 2012.

- a. The response acknowledges the difference in specifications and agrees to take the necessary steps to align the shelf life specifications for –b(4)-----

TT content as applied in --(b)(4)-- and the acceptance criterion for the -b(4)----- tetanus toxoid before -----(b)(4)----- in Belgium as a PMC. In the meantime, the firm feels that they can explain and justify the apparent discrepancy. The analytical methods used to assess the -----(b)(4)----- of TT are different between the ----(b)(4)--- manufacturing site in ----(b)(4)-- and the Belgian site. Due to the differences in these test procedures, the results obtained by the two methods should not be compared. (b)(4) lots of Purified TT have been tested in parallel according to both methods. Results show a bias of (b)(4) between the (b)(4) tests. Because of this bias, the firm considers it justified to have different acceptance criteria at both sites. Based on the average bias of (b)(4) between the (b)(4) methods, a stability specification of NLT (b)(4) in -(b)(4) is not substantially different from the specification of NLT (b)(4) in Belgium.

- b. The firm concludes that the stability specification of NLT (b)(4) in (b)(4)- is well within the percentage that is accepted for -----(b)(4)----- in Belgium when the bias is considered. Since Purified TT meet the acceptance criteria of NLT -----(b)(4)-----, the firm considers the -----(b)(4)--- shelf-life justified. Data was provided to show that lots up to an ----(b)(4)----- can be successfully ----(b)(4)-----.
- c. Based on the bias between the methods, the firm is convinced that the proposed shelf life claim of ----(b)(4)---- can be maintained with the proposed shelf-life specification of NLT (b)(4) . A release specification of NLT (b)(4) can not be applied because (b)(4) of the lots would fail to meet the release acceptance criteria. A specification of NLT (b)(4) has been proposed based on process consistency (See Item 11a).

Based on review of the firm's response, an additional information request was sent to the firm on 2 May 2012:

We have the following comments concerning your response to Question 2 of the IR sent 20 March 2012 (stemmed from Question 12 of CR letter dated 21 September 2011). We recognize that the analytical methods used to assess the -----(b)(4)----- of TT are different between the ----(b)(4)----- manufacturing site and the Belgian site. We also recognize that preliminary studies on (b)(4) lots show that the %TT using the ----(b)(4)----- method yield an average of approximately (b)(4) lower than that obtained by using the Belgian method.

- a. Please provide a detailed scientific explanation for the (b)(4) difference in results between the two sites.
- b. We do not concur with setting specifications and expiry dating using the justification of the (b)(4) bias based on testing of (b)(4) lots. Please revise your expiration date to -(b)(4)-- for Purified TT manufactured at -(b)(4)-- .

Please revise your release specification for Purified TT manufactured at (b)(4)- to not less than (b)(4)-.

- c. Please provide a detailed PMC for alignment of the two methods. Suggested wording is as follows:

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

The firm responded to this information request in Amendment 31 dated 9 May 2012.

- a. Several experimental parameters such as the -----(b)(4)----- procedure differ between the (b)(4) methods used in the ---(b)(4)--- and Belgian QC Labs that may be responsible for the (b)(4) bias. However, the parameter(s) that is/are responsible for the bias are not identified. There is no additional data available to provide a more detailed explanation of the bias.
- b. GSK accepts a -(b)(4)--- expiration dating for the purified TT bulk. This reduction in expiry dating has no impact on the launch lots AHCYA009A and AHCYA009B. These lots were manufactured with purified TT (b)(4) aged 6 and -(b)(4)---, respectively. In addition, GSK accepts to revise the release specification for the purified TT bulk manufactured in -(b)(4)-- to “not less than (b)(4)”
- c. GSK commits to align the methods used in both manufacturing sites to assess the -----(b)(4)----- TT so that the same method is used by both the --- (b)(4)--- and Belgian sites on the purified TT bulk. GSK will submit the ----
----- (b)(4) -----
-----.

Based on the review of all submitted information and the following PMC, the firm has adequately addressed my concerns.

PMC: ----b(4)-----

13. The ---(b)(4)----- MenY can be held for -----(b)(4)----- . A prior approval supplement will be required to -(b)(4)- this hold time from -----(b)(4)----- . ---(b)(4)----- at release, -----(b)(4)----- should be added to your proposed stability plan to support the -(b)(4)-- in hold time. Please acknowledge.

GSK acknowledged that a PAS will be required to -(b)(4)-- the hold time of --- (b)(4)----- MenY from -----(b)(4)----- . The stability plan that will be performed to support the -(b)(4)-- in hold time will include ----- (b)(4)----- . A sterility test will be performed at release and after -----(b)(4)----- .

Based on the review of all submitted information, the firm has adequately addressed my concerns.

14. Please explain how the Free Polysaccharide (PS) results provided in Tables 2 - 5 of your response to Item 66 are represented since some of the results are reported as absolute numbers and some are reported as a limit (i.e., (b)(4)). In addition, you state that the --(b)(4)- in Free PS for MenC-TT between time -b(4)-and subsequent time points and the --(b)(4)-- in Free PS for MenY-TT between time -b(4)- and subsequent time points is due to method variability. Please provide a detailed description of the investigation conducted to determine that the root cause is method variability. Also, the variability in your Free PS assays was not provided as requested. Please provide the assay variability for your -(b)(4)- assay in comparison to -----(b)(4)----- .

GSK stated that the --(b)(4)-- in Free PS for MenC-TT between time b(4) and subsequent time points and the --(b)(4)-- in Free PS for MenY-TT between time b(4) and subsequent time points is due to method variability. The variability of the free PS methods has been re-evaluated on “reconstituted samples” which are MenC-TT and MenY-TT conjugate (b)(4) samples containing free PS concentrations range from ---(b)(4)---- (MenC-TT) and --(b)(4)-(MenY-TT). Data are provided in the submitted validation report. Results of the variability are provided. The highest variability is observed on the lowest free PS concentrations because these concentrations are below or at the LOQ. The variability of the Free PS results obtained during stability of MenY-TT and MenC-TT lots are --(b)(4)----- . The variability of these data is within the variability as demonstrated during the validation study.

The assay variability for the (b)(4) assay in comparison to -----(b)(4)----- ----- was provided. It was demonstrated during product development that the polysaccharide antigenicity may depend on their size and/or conformation and can affect the accuracy of free polysaccharide quantification using an (b)(4) detection method. The free polysaccharide present in the conjugate bulks can potentially be heterogeneous in

size, therefore, the (b)(4) method was replaced with a -----(b)(4)----- method for QC release and stability studies of conjugate bulks.

The Free Polysaccharide results as determined by the -----(b)(4)----- methods are reported as absolute numbers and as a limit. The firm states that the values of free polysaccharide are reported as a limit when the result is less than the first calibration point.

Based on review of the submitted information, the following information was sent to GSK on 20 March 2012:

In your response to Question 14, you state that values for free polysaccharide are reported as a limit when the result is -----(b)(4)----- . For consistency, if the value for free polysaccharide is below the limit of quantitation it should be reported as < LOQ value (i.e., --(b)(4)-- for Hib-TT).

The firm responded to this information request in Amendment 27 dated 4 April 2012.

GSK responded that the free PS contents are now reported as a limit when the results are less than the limit of quantification. All results, below or above the LOQ, are expressed in %. The revised limits of quantification for the free PS content in MenC/Y-TT and Hib-TT are provided. For consistency, the stability data was recalculated based on the Free PS LOQ. I reviewed the provided data.

Based on review of the firm's response, an additional information request was sent to the firm on 2 May 2012:

We have the following comments concerning your response to Question 3 of the IR sent 20 March 2012 (stemmed from Question 14 of CR letter dated 21 September 2011).

- a. We recognize that the free PS contents are now reported as a limit when the results are less than the LOQ. The recalculated result for MenC-TT Batch -----(b)(4)----- for Free Polysaccharide C Content by ----(b)(4)----- is (b)(4)(Table 8). The LOQ is (b)(4). Please explain why this result is reported as -----(b)(4)-----.
- b. We note that the results for Free TT Content by (b)(4) and Free (b)(4) by ---(b)(4)-- are also reported as limits of varying results. Please confirm that this is for the same reason in that the result is reported as a limit when the result is -----(b)(4)----- . For consistency, if the value is below the LOQ it should be reported as < LOQ value. Please comment.

The firm responded to this information request in Amendment 31 dated 9 May 2012.

- a. GSK confirms that the result for MenC-TT Batch ---(b)(4)----- for Free PSC Content by ----(-b)(4)----- reported as (b)(4) is a typo and should be reported as < LOQ. The LOQ for this assay is -----(b)(4)----- . Revised tables are provided which shows that the result has been changed to (b)(4).
- b. For Free TT content on MenC-TT and MenY-TT by (b)(4), the protein content (as measured on the conjugate bulk at ---(b)(4)----- is used to calculate the -----(b)(4)----- , the free carrier content is expressed as -----(b)(4)----- . The first calibration point is at -(b)(4)----- and corresponds to the LLOQ as determined by the validation studies. The reason that the ---(b)(4)-- results expressed as limits may vary from bulk to bulk is due to the protein content that varies from bulk to bulk.

The free ---(b)(4)-- (mol/mol PS) on MenC-TT and MenY-TT is expressed as free -----(b)(4)----- . The -----(b)(4)----- is calculates as -----(b)(4)----- . If the free acetate content in μmol/mL is below the -----(b)(4)----- , the free (b)(4) content is expressed as -----(b)(4)----- . The first calibration point corresponds to the LLOQ as determined during the validation studies. The reason that the ---(b)(4)----- results expressed as limits may vary from bulk to bulk is due to the PS content that varies from bulk to bulk.

Based on the review of all submitted information, the firm has adequately addressed my concerns.

- 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.

GSK agreed to add -b(4)----- as a QC Release test for MenHibrix final container. This required development, a full validation of new assay, and the testing of clinical and commercial lots in order to establish specification. The SOP and validation report was provided for the test "--(b)(4)----- Content by (b)(4) in the MenHibrix final container vaccine". The review of the validation was performed by DBSQC. The acceptance criterion was based on data generated on clinical and commercial lots. The statistical approach used to calculate the acceptance criteria is based on process performance indices. The proposed acceptance criterion is between -----(b)(4)----- . I asked Freyja Lynn and Tsai-Lien Lin to perform a consult review on the adequacy of the statistical approach.

Based on the review of all submitted information, the firm has adequately addressed my concerns.

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.

GSK agreed to revise the --(b)(4)--- specifications on the MenC and MenY purified polysaccharide bulks and on the drug product. Separate specifications have been calculated for each PS bulk, based on available process data. The statistical approach used to calculate the acceptance criteria is based on process performance indices. The proposed specifications are -----(b)(4)----- PS (MenC PS), -----(b)(4)----- (MenY PS), and -----(b)(4)----- per dose on MenHibrix final container. In addition to the specifications, the firm has proposed alert limits. I reviewed the data submitted and asked Rajesh Gupta, Freyja Lynn, and Tsai-Lien Lin for a consult review in the adequacy in setting of specifications.

Based on review of the submitted information, the following information was sent to GSK on 20 March 2012:

In your response to Question 16, you provide the statistical method (process performance indices) used to calculate specification. Using this method for setting --(b)(4)--- specifications is not appropriate due to the high number of <LLOQ values. Assigning the <LLOQ values to be equal to the LLOQ values makes the estimated mean and thus the upper specification higher than it should be. Please set your --(b)(4)--- specifications using a scientifically justified method to ensure process consistency.

The firm responded to this information request in Amendment 27 dated 4 April 2012.

GSK acknowledged that a high number of <LLOQ values were obtained so far for the --(b)(4)--- content on the MenC and MenY purified PS bulks and on MenHibrix final containers. The firm considers that setting specifications close to or at the LLOQ are however not appropriate due to the analytical limitations inherent to the --(b)(4)--- test.

All available --(b)(4)--- contents for the (b)(4) lots of MenHibrix tested yield results --- (b)(4)-----. A scientific rationale was provided to support the new proposed specification of -----(b)(4)-----.

To date, --b(4)--- content obtained on MenC purified PS bulks are all ---(b)(4)-----
----- . A scientific rationale was provided to support the new proposed
specification of ----(b)(4)-----.

--(b)(4)--- contents obtained on (b)(4) lots of MenY purified PS bulks was provided.
--(b)(4)--- contents were often observed above the LLOQ of ---(b)(4)-----, with a
maximal value observed at ----(b)(4)----- . The specification was set based on
the distribution of current data. The model for the observed data should use an
appropriate statistical distribution and set the specification limit to a value close to
the 95 percentile. Given the high number of censored data ---(b)(4)---- , the
Weibull distribution was selected. Based on the Weibull distribution, 95% of the
data are below ---(b)(4)----- . Therefore, the new proposed specification ---(b)(4)--
-----.

I reviewed the data and consulted with Rajesh Gupta, Freyja Lynn, and Tsai-Lien
Lin. Based on the review of all submitted information, the firm has adequately
addressed my concerns.

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.

GSK agreed to assess polysaccharide content (Hib, MenC, and MenY) during on-going stability studies of commercial drug product. The PS content will be measured on commercial lots at the next time point ---(b)(4)---- . The firm submitted these results as part of their response to Item 19. In addition, GSK commits to include the PS content (Hib, MenC, and MenY) in the routine commercial stability program for MenHibrix final container future lots stored at 2-8 C -----(b)(4)-----
-----.

Based on the review of all submitted information, the firm has adequately addressed my concerns.

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

GSK is withdrawing the 0.9% sodium chloride diluent (b)(4) presentation and replacing it with a 0.9% sodium chloride diluent vial presentation manufactured by ----(b)(4)-----

------. Therefore, only one diluent presentation will be approved and this diluent vial presentation will be used during reconstitution of MenHibrix stability testing.

Based on the review of all submitted information, the firm has adequately addressed my concerns.

19. We do not concur with a 36 month 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)---.

The real time stability data up to 36 months was provided. All results obtained on the commercial final containers are within the acceptance criteria at all time-points up to 36 months. Based on real time stability data obtained on clinical and commercial final containers, GSK proposes a 36 month shelf-life for MenHibrix final containers.

Additional data was provided after storage of (b)(4) commercial final containers for 36 months at 2-8 C. These lots were tested directly after -----
------(b)(4)------. All testing data (pH, description, volume, (b)(4), Hib-TT Content, Total (MenC + MenY) Content, and MenY Content) measured directly -----(b)(4)----- the saline diluent meet the release specification for final containers after --- (b)(4) -- of storage. Testing data (pH, description, and (b)(4) measured after ----- (b)(4) -----
----- meet the release specification for final containers after --- (b)(4) -- of storage. However, testing of Hib-TT content on reconstituted product ----- (b)(4) -----
----- did not meet release specification. The firm is investigating the root cause of the OOS. They are examining the appropriateness of the specification of 80-120% for Hib-TT content in that the specification was set based on reconstitution in ----- (b)(4) -----
------. In addition, testing of Total (MenC + MenY) content and MenY content on reconstituted product ----- (b)(4) ----- experienced several invalid analytical runs. The root cause for these invalid runs is linked to the procedure used to prepare the (b)(4) samples. These OOS and invalid results led to further discussion on whether testing should be performed in ----- (b)(4) ----- and the appropriateness of specifications. See the separate section below for more discussion of this issue.

The current package insert states that reconstituted vaccine can be stored between 2 to 8 C for 24 hours prior to injection. Based on the above stability failure on reconstituted product stored at ----- (b)(4) -----, GSK proposes to update the product labeling to state that after reconstitution, MenHibrix should be administered immediately. GSK was asked to define “use immediately”. Data generated on the consistency lots support the immediate use of the reconstituted vaccine and its storage for ----- (b)(4) -----
------. Supporting data includes an evaluation of existing data provided in the 30 January 2012 amendment as well as new data provided in the 20 April 2012 amendment.

I performed a review of what we have approved in the past that states to reconstitute and use immediately in the package insert. Vaccines that have been approved with the instructions to reconstitute and use immediately include Menveo, Menomune, and Pentacel. Therefore, there is precedent in the use of “use immediately” without having a defined time limit.

I concur with the 36 month proposed expiry. I also concur with the package insert to state to use immediately after reconstitution. Based on the review of all submitted information, the firm has adequately addressed my concerns.

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.

GSK agreed to add sterility to the annual stability protocol of Hib-TT and sterility and --- (b)(4)-- testing to the annual stability protocol of MenC-TT and MenY-TT. (b)(4) lot of Hib-TT, MenC-TT, and MenY-TT will be placed on stability each year.

Based on the review of all submitted information, the firm has adequately addressed my concerns.

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.

GSK agreed to place (b)(4) lot of polysaccharide purified bulk (Hib, MenC, and MenY) on stability per year. -----(b)(4)----- will be tested for Hib, MenC, and MenY. ---(b)(4)----- will also be tested for MenC and MenY.

Based on the review of all submitted information, the firm has adequately addressed my concerns.

Additional CMC Issue (Testing in -----(b)(4)-----

The firm provided a document via email to David Staten on 10 April 2012. This document was then submitted as Amendment 30 on 2 May 2012. During vaccine development, the PS content of Hib-TT and MenC/Y-TT was performed at release of final container, but not part of stability. During this time, the assay was performed after reconstitution of final containers in (b)(4). During the review of the file, GSK agreed to assess routine stability of commercial lots with reconstitution in saline (the licensed diluent) instead of (b)(4). In addition, GSK agreed to add PS content to the routine

commercial stability program. At that time, the PS content tests were only validated in (b)(4).

Stability data --(b)(4)--- was provided as a response to Item 19 above. Testing of Hib-TT content on reconstituted product -----(b)(4)----- did not meet release specification. The firm is investigating the root cause of the OOS. They are examining the appropriateness of the specification of --(b)(4)--- for Hib-TT content in that the specification was set based on reconstitution in (b)(4) versus reconstitution in saline. In addition, testing of Total (MenC + MenY) content and MenY content on reconstituted product -----(b)(4)----- experienced several invalid analytical runs. The root cause for these invalid runs is linked to the procedure used to prepare the (b)(4) samples.

The validation of Hib-TT content after saline reconstitution was submitted in Amendment 26 dated 3 April 2012. The validation of the total (PSC+PSY) and PSY content after saline reconstitution was also submitted in Amendment 26 dated 3 April 2012. I defer the review of these validations to DBSQC.

It should be noted that the Hib-TT content, Total (PSC+PSY) content, and PSY content was originally validated and specifications proposed with reconstitution in (b)(4). During the review of this BLA, it was suggested to reconstitute in saline and not (b)(4). The firm agreed to do this and validated the assays. The firm is currently evaluating if the specifications for reconstitution in (b)(4) (not less than (b)(4) of the target dose) is appropriate for reconstitution in saline. Any changes to the current specifications will be submitted as a PAS after approval of MenHibrix. I do not expect a change in specifications based on reconstitution in (b)(4) versus saline. The firm specifically states that reconstitution in saline is performed for stability.

Based on the review of the information above, the following information request was sent to the firm on 2 May 2012:

You provided a document via email to David Staten on 10 April 2012. Please clarify the following.

- a. You state that PS Content stability testing (Hib, PSC, and PSY) is performed by reconstitution in saline. Please confirm that any final container testing (release or stability) is performed by reconstitution in saline.
- b. You state that specifications of PS content have been set based on reconstitution in (b)(4). You are currently evaluating if the specifications are appropriate for reconstitution in saline. Please explain why you anticipate the specification to change for the different reconstitution methods.

The firm responded to this information request in Amendment 31 dated 9 May 2012.

- a. The release for MenHibrix final container was planned in (b)(4) reconstitution except for the -----(b)(4)----- that is performed with saline reconstitution. All tests performed for routine commercial stability of MenHibrix final container (b)(4) lot per year) are planned in saline reconstitution. CBER requested during a teleconference held on 3 May 2012 that the entire release program of the final containers be performed in saline reconstitution.

Tests already performed and validated with saline reconstitution include the following.

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

GSK proposes to implement the following testing in saline reconstitution instead of (b)(4) for all commercial lots.

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

GSK proposed to maintain the release in (b)(4) for the following tests until the impact of the reconstitution in saline of the methods and/or acceptance criteria has been fully documents.

- For ---(b)(4)---, no impact of saline reconstitution is expected. The acceptance criteria will require some re-evaluation as the ---(b)(4)--- of a 0.9% NaCl solution is ---(b)(4)---. The acceptance criteria will be evaluated on all available MenHibrix final containers. The procedure and revised acceptance criteria will be submitted as a PAS in Q4 2012.
- -----(b)(4)----- was developed and validated in (b)(4). A potential impact of saline reconstitution cannot be excluded. A comparability study will be performed to assess the impact of the saline reconstitution on the method. Based on the results obtained, it will be decided whether some requalification or revalidation are required. Once the impact on the method is documented, the impact on the acceptance criteria will be evaluated. The revised method

and revised acceptance criteria, if applicable, will be submitted as a PAS in Q4 2012.

GSK proposed that the current procedures are adequate and can be used as such for the release of MenHibrix final containers.

- The –b(4)---- content by ----(b)(4)---- is performed without reconstitution of the lyophilized vaccine.
- The --(b)(4)--- content test is intended to detect potential contamination of the final container and the procedure was validated in –b(4)- reconstitution. The --(b)(4)--- content is also measured for release of the commercial saline diluent. Therefore, the combined --(b)(4)--- is adequately controlled through the --(b)(4)--- measured independently.
- The sterility tests are intended to detect potential contamination of the final container and the procedures were validated in --(b)(4)----- reconstitution. The sterility is also tested for release of commercial saline diluent. Therefore, the combined sterility is adequately controlled through the --(b)(4)--- measured independently.
- The sucrose content is measured –b(4)----- in (b)(4). The sucrose is used as a stabilizer and -----(b)(4)----. Consequently, the quantification of sucrose content –b(4)----- in (b)(4) is fully adequate to demonstrate the consistency.

- b. The proposed package insert instructions were revised based on an OOS for PS Content for Hib-TT for MenHibrix reconstituted with saline and -----(b)(4)----- . The root cause for this OOS is still being investigated. A potential root cause for this OOS is the appropriateness of the specification for reconstitution in saline versus (b)(4). This is currently being investigated. No data has been obtained yet to prove this root cause.

Based on the review of all submitted information and the following PMCs, the firm has adequately addressed my concerns.

PMC: -----

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

PMC: -----

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

Additional CMC Issue (Outstanding PMC):

Based on the review of the outstanding PMCs submitted in the original BLA or as a response to the CR letters, the following information request was sent to the firm on 2 May 2012:

You provided the following PMC in your response dated 15 April 2011.

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

Revised wording of the PMC is suggested below. Please provide a date when you anticipate being able to submit the review of specification.

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

The firm responded to this information request in Amendment 31 dated 9 May 2012.

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

Based on the review of all submitted information and the following PMCs, the firm has adequately addressed my concerns.

4 pages redacted due to (b)(4)

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

2. -----(b)(4)-----.
3. -----
------(b)(4)-----.
4. -----
------(b)(4)-----
-----.

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

42-49 FINAL CONTAINER BLA - Hib-MenCY-TT Final Container

1. Sucrose by (b)(4) should be added. Specification = ----(b)(4)-----.
2. ---(b)(4)--- should be added. Specification = ----(b)(4)-----.
3. -----(b)(4)-----should be added. Specification = ----(b)(4)-----.
4. On page 43, the test is written as polysaccharide C content by --(b)(4)-- with a specification of not less than (b)(4) of the target value. The BLA states that polysaccharide C content is determined by calculation with a specification of not less than (b)(4).
5. On page 44, please add the word “Total” in front of polysaccharides PSC-PSY content by (b)(4).
6. On page 46, the ---(b)(4)----- is stated to be determined by -----(b)(4)-----.
The BLA states ---(b)(4)-----.
7. On page 48, the ---(b)(4)---specifications are not more than ----(b)(4)-----.
We are currently reviewing a specification of -----(b)(4)-----e.

The firm responded to this information request in Amendment 31 dated 9 May 2012. The firm provided a draft LRP as part of this amendment in response to the items above. I reviewed the LRP and found most of the above items have been adequately addressed. Based on my review, I still had the following concerns that were provided to the firm during a teleconference on 14 May 2012.

1. There were changes to the specification from the first version of the LRP to this version for the following tests. I did not see that these changes were requested or communicated in the BLA.
 - -----(b)(4)-----

 - -----(b)(4)-----
 - -----(b)(4)-----
 - -----(b)(4)-----
 - -----(b)(4)-----
 - Final Container – PS Content for MenC
 - Final Container – PS Content for MenY

- Final Container – PS Content for MenC-Y
 - Final Container – PS content for Hib
2. The following comments were not addressed or incorrectly address in this version of the LRP.

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

The firm responded to this information request in Amendment 32 dated 16 May 2012. This amendment contains the updated LRP along with four associated history tables which document where the associated test methods and acceptance criteria in the LRP were filed to the MenHibrix BLA. These tables are for the following.

- Hib-TT and –b(4)-----
- MenC-TT and –b(4)-----
- MenY-TT and –b(4)-----
- Final Bulk and Final Container

I reviewed the updated LRP and the associated tables. Based on my review, I still had the following concerns that were provided to the firm during a teleconference on 23 May 2012.

1. For MenHibrix final container, the LRP states that the ---b(4)--- is determined by ----b(4)------. The table of the release tests for MenHibrix submitted in Amendment 31 (5/9/12) also states that the –b(4)-content is determined by ----b(4)------. The BLA and the submitted SOP states that the ----b(4)----- is determined by ----b(4)------. Please verify which is correct and fix what it is not correct so that they match.
2. There is an error on the table on page 5 of the LRP. The box that reads MenC PS Purified Bulk (on the right) should read MenY PS Purified Bulk.
3. There is an error in the History Specification Change for MenC-TT and - b(4)-----table. The table lists that the specification for (b)(4) for MenC-

diluent and vaccine. The lot number used on the kit carton will be a unique lot number as shown in the example below. The kit carton will be imprinted with all labeling except the lot and expiry dating. The lot

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

----. The kitting process will take place in --(b)(4)-- on a ----(b)(4)----- packaging line which does not have imprinting capabilities.

Antigen Batch #	Diluent Batch #	Combo Batch #
----b(4)-----	-----b(4)-----	-----b(4)-----
--b(4)-----	-----b(4)-----	-----b(4)-----
--b(4)-----	-----b(4)-----	-----b(4)-----

- Email dated 10 May 2012 from N. Pyle to K. Prutzman, D. Staten, and J. Temenak: Demo labels were provided to assist in the review of the labeling as shown below. The auxiliary label can not be moved from its current positioning without delays. The firm proposed a PMC to change to -----(b)(4)----- . The firm is suggesting a CBE-0 but I would recommend a CBE-30 at a minimum.

Combo Box	-----b(4)-----	Exp 06/13/2013
Vaccine Box	-----b(4)-----	Exp 01/01/2015
Vaccine Vial	-----b(4)-----	Exp 01/01/2015
Diluent Box	-----b(4)-----	Exp 06/13/2013
Diluent Vial	-----b(4)-----	Exp 06/13/2013

- Email dated 11 May 2012 from N. Pyle to D. Staten, K. Prutzman, and J. Temenak: GSK proposes to implement -----
 -----(b)(4)-----
 ----- . This time is needed by ordering/receipt and validation of the -----(b)(4)----- .

- Email dated 15 May 2012 from N. Pyle to J. Temenak: One lot number is to be used for the vaccine carton, vaccine vial, and auxiliary label (Lot -----b(4)----- in above example). The expiration dating on the auxiliary label is the shortest dating between the diluent and the vaccine. The auxiliary label could not be moved so as not to be performing the function of a temper-evident seal without delays in that a physical location of labeling would need to be changed to accommodate a space. The vaccine vials that come from Belgium are received in --(b)(4)-- as unlabeled vials. --(b)(4)-- performs all labeling and packaging for the vaccine. The combo batch number is assigned through SAP (controlled database).

I have reviewed the information provided in the submission and the emails above. There have been many high level discussions on the path forward for labeling of MenHibrix.

The firm is providing a unique combination lot number for the kitted box. However, this lot number and expiry date are not imprinted on the box but is on an auxiliary label which is placed on the box and used as both a label and a tamper-resistant seal. The concern is that upon opening the box, the seal and lot number will be destroyed. There were concerns with tracking adverse events with the destruction of this label. After many conversations, it was determined that whether the vaccine lot number or the combination lot number is recorded from the vaccine vial, AE tracking can occur. It may just be more labor intensive with the vaccine vial lot number. The firm is not able to move the label because that part of the box is treated in such a manner that makes the sticker unable to be removed. I am in agreement to approve using an auxiliary label for the outer kit lot number and expiry with a PMC for the following.

PMC: -----
----- (b)(4) -----

-----.

The other area of concern with labeling of MenHibrix is what lot number and expiry dates are to be used. The diluent is manufactured and labeled by ----- (b)(4) -----
----- . The diluent is then shipped to --(b)(4)--- for packaging. The vaccine is manufactured in Belgium and sent to -(b)(4)-- as unlabeled vials. The unlabeled vials are labeled at--(b)(4)--- and then copackaged with the diluent. The diluent lot numbers and expiry are assigned by --(b)(4)---. The vaccine lot number and expiry is assigned in Belgium. The kitted lot number is assigned in SAP and the expiry date of the kitted package is assigned as the shorter of the two components. The question is which lot number should be used on the vaccine vial and vaccine carton (vaccine lot number or kitted lot number). In addition, which expiry date should be applied to the vaccine vial (vaccine expiry or kitted expiry). The below summarizes the issues that were discussed extensively with Management.

History of Menomune and ActHib

I checked to see what we did for Menomune and ActHib. These are the most representative since they are a vaccine copackaged with a diluent. Pentacel and Menveo are slightly different since it is a vaccine used to reconstitute another vaccine. For both Menomune and ActHib, I have confirmed the following:

The vaccine vial is labeled with the vaccine lot number and the vaccine expiry date.

The diluent vial is labeled with the diluent lot number and the diluent expiry date.

The copackaged material is labeled with a combo lot number and the shortest expiry of the two components. For Menomune and ActHib, this is always the vaccine expiry date since the diluent has a much longer expiry.

History of Menveo and Pentacel

that of the kitted vaccine. I am not suggesting that we tell the manufacturers how to assign lot numbers. I am suggesting that when a lot number and expiry are placed on the label, the correct expiry date - lot number combination be used. Using the example above, the vaccine has a lot number of -----(b)(4)---- with an expiry of 2015 and the kitted material has a lot number of -----(b)(4)---- with an expiry of 2013.

Based on recent emails, the vaccine expiry date should not be shortened to match the kitted vaccine expiry date. Therefore, the simplest fix to my concern would be to ask the firm to place the lot number of the vaccine on the vaccine vial instead of the kitted lot number. As for our example, the vial will be labeled with lot number -----(b)(4)---- with an expiry of 2015.

Based on the review of the submitted information to the file and in emails and well as much internal discussion, the following concern was communicated with GSK on 23 May 2012.

The combination lot number is used on the combination box, the vaccine box, and the vaccine vial. This same combination lot number is associated with two different expiry dates (2015 on the vaccine vial and vaccine box and 2013 on the combination box as shown in the examples provided). This has potential for confusion by the end user. Please use the vaccine lot number in place of the combination lot number on the vaccine vial label. The firm voiced some concerns in that there were reasons why they wanted the combination lot number on the vaccine vial. It was stated that the labeled lot numbers needed to match their corresponding expiry dates. Therefore, if the combination lot number were to stay on the vaccine vial, and then the combination expiry would need to be used.

The firm responded to this IR in Amendment 35 dated 4 June 2012. The expiration date assigned to the combo box will be the shortest dating between the diluent and the vaccine. The vaccine will have just one lot number and one expiration date documented on all three kit components. Thus the same vaccine lot number and the same vaccine expiration dating will be on the vaccine vial label, the vaccine inner carton, and the combo box. The following information summarizes the process.

Diluent Carton and Vial Label

Batch number: ---(b)(4)---

Expiry date: expiry date of the diluent

Combo Box

Batch number: ---(b)(4)---

Expiry date: earliest date between expiry date of diluent and expiry date of vaccine

Vaccine Carton and Vial Label

Batch number: ---(b)(4)--- (same as on combo box)

Expiry date: earliest date between expiry date of diluent and expiry date of vaccine (same as on combo box)

An updated vaccine inner carton label and combination box label are provided. In addition, a set of demonstration labels are provided as an example as to how lot numbers and expiry dating will be assigned for the combo box and its components.

Based on the review of the submitted information, the firm has adequately addressed my concerns about how lot numbers and expiry dating will be assigned for MenHibrix.

In addition to the above, I reviewed the storage temperatures on the proposed package insert and carton labeling. The firm proposes the following for both.

Vaccine – Store refrigerated between 2 °C and 8 °C (36 °C and 46 °C). Protect vials from light.

Diluent – Store refrigerated or at controlled room temperature between 2 °C and 25 °C (36 °C and 77 °C). Do not freeze. Discard if the diluent has been frozen.

Please note that this is different than what was previously approved for Hiberix as shown below.

Vaccine – Store refrigerated between 2 °C and 8 °C (36 °C and 46 °C). Protect vials from light.

Diluent – Store refrigerated between 2 °C and (b)(4) (36 °C and (b)(4)) or at a controlled room temperature between (b)(4) and 25 °C ((b)(4) and 77 °C). Do not freeze. Discard if the diluent has been frozen.

The kitting process originated for MenHibrix in conjunction with the use of --(b)(4)-- saline diluent in vials and packaging being now performed in ---(b)(4)----. These changes were submitted in Amendment 21. Hiberix was not originally approved as a combination kit of vaccine and saline. They were packaged and shipped separately. There were concerns in that there is no data to support the temperature range of --(b)(4)--. These concerns were voiced to the firm by J. Temenak on 1 June 2012. The firm responded with the following.

The firm bracketed the entire temperature range by conducting stability studies at both 2-8 °C and --(b)(4)-- ranges. Therefore, the --(b)(4)-- range is bracketed.

I continue to believe that the current Hiberix label is optimal since it reflects most accurately the conditions of study. However, (b)(4) bracketing recommendations would appear to apply. Therefore, I see no reason to object to their current proposal of --(b)(4)--.

Based on the review of all submitted information, the firm has adequately addressed my concerns on the package insert and vial/carton labeling.

PMCs:

The following PMCs were requested as part of approval. These PMCs were communicated to GSK on 29 May 2012 in an email from K. Prutzman to N. Pyle and J. Gould.

1. -----
----- (b)(4) -----

2. -----
----- (b)(4) -----

3. -----
----- (b)(4) -----

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

5. -----
----- (b)(4) -----

The firm responded to the PMC request in Amendment 34 dated 4 June 2012. The firm slightly changed the wording on PMC number 2. The revised wording of the PMC is shown below.

I concur with the revised wording. In addition to the above, there was one additional CMC PMC concerning extractable/leachable studies. This PMC was requested by another reviewer. I will defer the acceptability of the wording for that PMC to R. Ballica.

In Amendment 36 dated 12 June 2012, GSK slightly revised PMC number 2. The revised wording is shown below.

I concur with the revised wording. The final PMC list requested from my review is provided in the Recommendation section below.

Recommendation:

Based on review of all information submitted to the file, I recommend approval of MenHibrix with the following PMCs submitted in Amendment 35 dated 4 June 2012 and Amendment 36 dated 12 June 2012. MenHibrix will be manufactured in --(b)(4)-- and Belgium, formulated and filled in Belgium, and labeled and packaged in ---(b)(4)---. The expiry of MenHibrix vaccine will be 36 months when stored at 2-8 °C. Diluent (0.9% NaCl) will be manufactured, labeled, and packaged at -----(b)(4)----- . The expiry of Diluent will be 24 months when stored at 2-25 °C. The primary packaged MenHibrix vaccine and primary packaged 0.9% NaCl Diluent will kitted in ---(b)(4)----. The expiry of the kitted MenHibrix will be the earliest date between expiry date of diluent and expiry date of vaccine.

PMCs:

1. -----

2. -----

3. -----
----- (b)(4) -----

4. -----

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

5. -----

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

