

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

MEMORANDUM

Date: May 4, 2010

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

Through Milan Blake, Ph.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
Amendment 3, dated 8 February 2010
Amendment 4, dated 3 March 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[®]. 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 has not been defined in the BLA. This will need to be provided. See CR comment #1 below.

Residual formaldehyde is measured on ----(b)(4)---- during QC release. From a calculation performed considering worst case scenario, the maximum amount of formaldehyde per vaccine dose of Hib-MenCY-TT is 0.72 µg. This is needed for the label. I asked another reviewer (W. Vann) to evaluate this calculation and he found it to be acceptable.

Review of Hib-TT Drug Substance:

Manufacture of Hib-TT Drug Substance:

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Critical Manufacturing Steps and Intermediates:

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Process Validation and/or Evaluation:

Process validation was achieved through demonstration of process consistency for at least (b)(4) batches that must show compliance with the pre-established quality standards. Manufacturing of these batches must also show acceptable consistency of the --- (b)(4) --- performances, of the residuals clearance profiles and of the manufacturing yields. Process validation was also achieved through the identification of the manufacturing process critical parameters. A parameter is considered to be critical when operating beyond its acceptance range has an impact on the safety or efficacy of the final product. Critical process parameters are either validated or the performance of the production step in which these critical parameters operate are controlled to guarantee robustness.

The manufacture of Hib was validated by evaluating the consistency of the -----

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Manufacturing Process Development:

A summary of the manufacturing process development of the Hib-TT conjugate is provided in the table below. Each of these changes has been validated by the production and control of at least (b)(4) validation batches. The data provided demonstrate validation of the changes.

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Reference Standards and Materials:

A listing of the current reference standards and reference materials used in the QC testing are summarized in the table below. The stability of QC reference standard materials is

monitored on an ongoing basis by the use of an internal control. The internal control is a lot representative of the standard tested as unknown in parallel to the analyzed samples. Each time an assay is conducted; the test result for the internal control is analyzed and compared to an established consistency range. A trend analysis of the internal control test results is conducted every (b)(4) months. The analysis is documented and approved by the QC supervisor in charge of the test. Any trend toward an out of consistency for the internal control would trigger an investigation and corrective action may be taken. Future reference lots produced in house needs to pass all the QC release tests. The determination of the titer of a new reference standard batch should be based on a minimum of (b)(4) independent measurements, unless properly justified and approved by QA.

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Hold Time Validation/Stability:

The relationship between MenC, TT, and MenC-TT commercial consistency and clinical consistency batches are shown in the table below.

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(b)(4)

Hold Time Validation/Stability:

The relationship between MenY, TT, and MenY-TT commercial consistency and clinical consistency batches are shown in the table below.

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Review of Drug Product:

Composition:

The MenHibrix final container vaccine is presented as a lyophilized preparation in -----(b)(4)- glass vials sealed with a rubber closure and flip off caps. Hib-MenCY-TT vaccine contains three polysaccharides, each conjugated to Tetanus toxoid, coded Hib-TT, MenC-TT, and MenY-TT. Sucrose and Tris-HCl are excipients. Sucrose acts both as a -----(b)(4)----- . Tris-HCl (b)(4) buffer allows a stable physiological (b)(4). Each vial of MenHibrix vaccine is reconstituted with the content of a --(b)(4)----- containing 0.9% Sodium Chloride Injection. A ----(b)(4)----- is implemented during the formulation of the Hib-MenCY-TT final bulk in order to guarantee an effective injectable dose of 0.5 mL containing 2.5 µg of Hib and 5 µg of MenC and MenY polysaccharides. The --(b)(4)--, which is a concentration (b)(4), has been applied in order to balance the loss of immunogenic material that occurs when the -----(b)(4)----- and subsequently injected.

The immediate packaging materials used for the container-closure system are equivalent to those used for other vaccines manufactured by GSK. Composition of the MenHibrix lyophilized vaccine reconstituted with saline diluent is presented in the table below.

Table 1 Quantitative composition for Hib-MenCY-TT vaccine

Ingredients	Quantity (per dose 0.5 mL)	Function	Reference to quality standards
Active ingredients			
Conjugate of <i>Haemophilus influenzae</i> type b capsular polysaccharide and tetanus toxoid (mean TT/PS ratio: 2.5)	2.5 µg Hib ~ 6.25 µg TT	Immunogen	(b)(4)
Conjugate of <i>Neisseria meningitidis</i> C capsular polysaccharide and tetanus toxoid (mean TT/PS ratio: 1)	5 µg MenC ~ 5 µg TT	Immunogen	(b)(4)
Conjugate of <i>Neisseria meningitidis</i> Y capsular polysaccharide and tetanus toxoid (mean TT/PS ratio: 1.3)	5 µg MenY ~ 6.5 µg TT	Immunogen	(b)(4)
Excipients			
1. Lyophilized with active substance			
Sucrose	12.6 mg	Stabilizer and	(b)(4)
Tris (Trometamol)-HCl pH (b)(4)	96.8 µg	(b)(4)	(b)(4)
Diluent			
NaCl	(b)(4)	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)	(b)(4)

- Pharmaceutical form: lyophilized product, to be reconstituted with saline diluent before injection
- Presentation: monodose in (b)(4) glass vials
- Administration: intramuscular injection
- Storage: +2°C to +8°C
- Overfill: a formulation (b)(4) of approximate (b)(4) applied in order to guarantee an effective injectable dose of 0.5-ml containing 2.5 µg of Hib, 5 µg of MenC and MenY polysaccharides.
- Abbreviations: (b)(4)
Hib (or PRP) = capsular polysaccharide (Polyribosyl Ribitol Phosphate)
TT = Tetanus Toxoid

Manufacturing Development:

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Control of Excipient:

The only ingredients other than the active substances are sucrose and Tris. Each of these excipients is tested according to the current -----(b)(4)-----.

Control of Drug Product:

The QC release specifications are outlined in the following tables as presented in the original BLA. Several specifications were missing as QC Release tests. These tests either need to be developed and validated or the classification of an existing test needs to be from monitoring or Quality Decision to Quality Release. Specifications have been established using information from the testing of development and commercial batches.

The limits proposed in the ----(b)(4)---- and WHO TRS N°897 was also taken into consideration. A description of the tests and a summary of the validation data are included in the file.

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Stability:

MenHibrix vaccine stability has been assessed by long term, real-time stability studies, accelerated stability studies and after reconstitution of the vaccine with the saline diluent. Based on the data, GSK is requesting an expiration dating period of 36 months at 2-8°C.

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Review of Lot Release Protocol:

The proposed lot release protocol is included in the file. I reviewed the lot release protocol for the following:

- Is all the required information needed for approval of CBER lot release provided in the protocol?
- Is the lot release protocol consistent with other licensed US products?

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General CMC Comments to be included in CR Letter:

1. 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 if it is possible to perform an investigation and still use the product. See CR comment #2.
2. In Amendment 3 dated 2/12/2010, you state that any changes in reference material for Hib-TT, MenC-TT, MenY-TT, and Hib-MenCY-TT testing would be communicated to the agency in your Annual Report. We would need a detailed comparability protocol (CP) for this to qualify for annual reporting. Please include a detailed comparability protocol or alternately, submit a detailed CP as a prior approval supplement after licensure. See CR comment #30.
3. In Section 3.2.P.2, you state that the Free PS 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 PS contents assessed by chemical methods (b)(4)- for Hib-TT, (b)(4) for MenC-TT, (b)(4)- for MenY-TT) are proposed to (b)(4)- based method at the level of the (b)(4)- is proposed to (b)(4)- based method on drug product.
 - a. Appropriate bridging studies should be performed to (b)(4) the Free PS 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 (section 3.2.S.2.3). Please provide additional data comparing these two methods.
 - b. In Section 3.2.S.7.3, you provide stability data of commercial bulk conjugate lots. We note that free polysaccharide C content by (b)(4) shows a (b)(4)- between your time-(b)(4) testing and the (b)(4)-month and (b)(4)-month time points. We also note that free polysaccharide Y content by (b)(4)- shows an (b)(4)- between your time-(b)(4) testing and the (b)(4) month and (b)(4)-month time points. Please provide an explanation for these results and the variability in your assays.
 - c. The specifications for Free PS 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 PS by (b)(4)- of MenY-TT to not more than (b)(4) or provide a detailed justification for this change in specification.
 - d. The proposed (b)(4)- also uses an (b)(4) based method. Please justify the use of this method based on your observation that the (b)(4) method is not accurate.

- e. All clinical lots were released using the (b)(4) based method. Please comment on the effect of an inaccurate release method on your clinical studies.
- f. You propose to replace the Free PS by -(b)(4)- with -----(b)(4)----- for drug product. Please provide a detailed summary to support that -----(b)(4)----- are accurately measuring Free PS for Hib, MenC, and MenY.
- g. Please provide validation data that demonstrate that the -----(b)(4)----- and ---(b)(4)--- assays are stability indicating.

The change in Free PS assay affects all drug substances (Hib-TT, MenC-TT, and MenY-TT) as well as drug product. This affects both release and stability testing. See CR comment #19 below.

Recommendation:

Based on the review of all the submitted information, I would not recommend approval of MenHibrix vaccine at this time. I have the following items that should be included in a CR letter.

CR Comments:

General

1. Please provide information specifying how the date of manufacture is determined with respect to the expiration dating period for MenHibrix. For example, please specify if the date of manufacture is calculated from the date of ----(b)(4)-----, the date of filling into final containers or some other measure. In addition, please provide the date of manufacture for the sterile diluent manufactured at GSK.
2. 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 if it is possible to perform an investigation and still use the product.

Drug Substance

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Drug Product

16. We request that you add the following as QC Release Tests for the MenHibrix final container (Section 3.2.P.5.1) in order to ensure the safety, purity, and potency of the final drug product:
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 - b. --- (b)(4)---
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 - g. --- (b)(4)---
17. --- (b)(4)--- is included as a QC release specification during different stages of manufacture. You indicate that your proposed --- (b)(4)--- 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 provide a detailed justification for each of the following proposed specifications including an explanation of why the specifications are not reflective of actual validation data.
- a. In Section 3.2.S.2.4, the --- (b)(4)--- specification for *N. meningitidis* Serogroup C Polysaccharide is “not more than ----- (b)(4)-----”. However, the batch analysis data shows that --- (b)(4)--- batches have an --- (b)(4)--- level of ----- (b)(4)----- and the remaining batch has an --- (b)(4)--- level of ----- (b)(4)-----.

- a. In Section 3.2.S.2.4, the ---(b)(4)--- specification for *N. meningitidis* Serogroup Y Polysaccharide is “not more than -----(b)(4)-----”. However, the batch analysis data shows that ---(b)(4)--- batches have an ---(b)(4)--- level of ----(b)(4)----- and the remaining (b)(4) batches have an ---(b)(4)--- level of -----(b)(4)-----.
 - b. In Section 3.2.P.5.1, the endotoxin specification for MenHibrix final product is “not more than ----(b)(4)----”. However, the batch analysis data shows that the endotoxin levels are always ----(b)(4)----.
18. In Section 3.2.P.3.5 (Process Validation and/or Evaluation – Hib MenCY-TT) you propose a hold time of (b)(4) of the formulated bulk. However, you only have data from (b)(4) commercial lot with a hold time of (b)(4). We do not agree that hold time 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 revise your hold time in accordance with the maximum dating for (b)(4) lots of commercial product, or provide data from (b)(4) additional commercial lots held for (b)(4) to support this hold time.
19. In Section 3.2.P.2, you state that the Free PS 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 PS 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 (TR).
 - g. Appropriate bridging studies should be performed to change the Free PS 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 (section 3.2.S.2.3). Please provide additional data comparing these two methods.
 - h. In Section 3.2.S.7.3, you provide stability data of commercial bulk conjugate lots. We note that free polysaccharide C content by -(b)(4)- shows a (b)(4) between your time-(b)(4) testing and the (b)(4)-month and (b)(4)-month time points. We also note that free polysaccharide Y content by ---(b)(4)--- shows an (b)(4) between your ---(b)(4)--- testing and the (b)(4)-month and (b)(4)-month time points. Please provide an explanation for these results and the variability in your assays.
 - i. The specifications for Free PS 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 PS by ---(b)(4)--- of MenY-TT to not more than (b)(4) or provide a detailed justification for this change in specification.

- j. 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.
 - k. All clinical lots were released using the (b)(4) based method. Please comment on the effect of an inaccurate release method on your clinical studies.
 - l. You propose to replace the Free PS by -(b)(4)- with -----(b)(4)----- for drug product. Please provide a detailed summary to support that -----(b)(4)----- are accurately measuring Free PS for Hib, MenC, and MenY.
 - g. Please provide validation data that demonstrate that the -----(b)(4)----- and (b)(4) assays are stability indicating.
20. In Section 3.2.P.5.2, you provide the polysaccharide content specifications for MenHibrix final product. Please revise your polysaccharide specifications as follows:
- a. The specification for Hib content for MenHibrix is not less than (b)(4) of the target value. Please revise these specifications to between ---(b)(4)--- per dose.
 - a. The specification for Total PSC-SPY content for MenHibrix is not less than (b)(4) of the target value. Please revise these specifications to between ---(b)(4)--- per dose.
 - b. The specification for Total PSY content for MenHibrix is not less than (b)(4) of the target value. Please revise these specifications to between (b)(4) and (b)(4) per dose.
 - c. The specification for Total PSC content for MenHibrix is not less than (b)(4) of the target value. Please revise these specifications to between (b)(4) and (b)(4) per dose.
21. In Section 3.2.P.5.1, you provide the QC Release Specifications for MenHibrix final product. Please specify how you will address diluents manufactured by both GSK and by -----(b)(4)----- for reconstitution for release testing.

22. In Section 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. Please address the following with respect to these studies:
- Please explain why Free Polysaccharide (Hib, MenC, and MenY) are not being evaluated.
 - We do not agree with your plan to assess Polysaccharide Content (Hib, MenC, and MenY) at only the time -----(b)(4)----- time points. Please revise your protocol to include these assays at each time point.
 - Your specification for ---(b)(4)--- content is listed as not more than (b)(4) IU/dose. Please provide a justification for this specification based on actual data obtained in your process development studies.
23. In Section 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)----- (Hib, MenC, and MenY). Please repeat this study evaluating these additional parameters. In addition, in Section 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 address both diluents manufactured by GSK and by -----(b)(4)-----.
24. In Section 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. Please provide additional data for your commercial stability lots, and propose a revised expiration dating based on these data.
25. Section 3.2.P.8.2.3 (Stability, Hib-MenCY-TT) - Please provide a plan/protocol to perform on-going annual stability studies on (b)(4) lot of Hib PS, MenC PS, MenY PS, 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 should not be the same lot which is used to manufacture the Menhiberix final container placed on stability.
26. In Section 3.2.P.8.2 (Post-approval Stability Protocol and Stability Commitment - Hib-MenCY-TT) you provide a protocol for on-going stability studies of commercial drug product post-approval. We note that you have not included Free

- Polysaccharide (Hib, MenC, and MenY), Polysaccharide Content (Hib, MenC, and MenY), or ---(b)(4)--- content in your proposed stability studies. Please revise your protocol to include these assays at each time point.
27. In Section 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: the temperature of the studies has been changed from -----
----- (b)(4) ----- have been deleted from the protocol. Please provide a justification for these proposed changes.
 28. In Section 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 ----- (b)(4) ----- than is currently used for the manufacturing of the diluent. We request that you revise your expiration dating for the diluent to be reflective of stability data collected with the current manufacturing process and container/closure system for the diluent (e.g. ----- (b)(4)--). Alternatively you may provide additional stability data in support of your proposed --- (b)(4) --- expiration date.
 29. In Section 3.2.P.5.4, you provide batch analysis data for 0.9% sodium chloride diluent using the current process for the US market. 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.
 30. In Amendment 3 dated 2/12/2010, you state that any changes in reference material for Hib-TT, MenC-TT, MenY-TT, and Hib-MenCY-TT testing would be communicated to the agency in your Annual Report. We would need a detailed comparability protocol (CP) for this to qualify for annual reporting. Please include a detailed comparability protocol or alternately, submit a detailed CP as a prior approval supplement after licensure.
 31. The package insert states that MenHibrix should be administered within --- (b)(4) -- of reconstitution. After reconstitution, the vaccine should be stored refrigerated ----- (b)(4) ----- between 2 and - (b)(4) -. You do not have sufficient data to support a storage time of (b)(4) for reconstituted vaccine. Please revise the storage temperatures in your package insert.