



DEPARTMENT OF HEALTH & HUMAN SERVICES
FDA/CBER/OVRR/DBPAP

Food & Drug Administration
1401 Rockville Pike
Rockville, MD 20852

MEMORANDUM

Date: May 5, 2010

To: File for 125363/0

From: Daron Freedberg, Ph.D.
OVRR/DBPAP/LBP

Through: Willie Vann, Ph.D., Chief,
OVRR/DBPAP/LBP

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

Sponsor: GlaxoSmithKline (GSK)

SUBMISSIONS REVIEWED

STN 125363/0 Original BLA
STN 125363/0.1 (amendment received 8/27/2009)
STN 125363/0.3 (amendment received 2/12/2010)
STN 125363/0.4 (amendment received 3/3/2010)

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 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 covalently bound to tetanus toxoid.

MenHibrix is a lyophilized vaccine 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 0.9% Sodium Chloride diluent. The reconstituted product contains 2.5 µg of PRP-TT, 5 µg PSC-TT and 5 µg PSY-TT per 0.5 mL dose volume.

Sucrose is added as an --(b)(4)-- as a stabilizer and ---(b)(4)----- Tris-HCl ---(b)(4)--- is also added as an -----(b)(4)----- Sucrose and Tris are lyophilized with the active substances in the vaccine. The sucrose content per 0.5 mL dose is 12.6 mg, and the Tris content per 0.5 mL dose is 96.8 µg.

GSK is proposing an expiration dating period of 36 months at +2 to +8 °C for MenHibrix final container vaccine. However, the firm has not provided information regarding on how the date of manufacture is determined (i.e., the start date of filling into final containers). This firm should provide this information.

MenHibrix is not currently licensed in any country or region. The clinical package to support licensure of *MenHibrix* consists of 13 completed Phase II and III clinical studies. These studies were conducted in the United States (US), Australia, Belgium, Germany, and Mexico. The submission also includes safety data obtained in two ongoing studies, both conducted in the US.

MenHibrix is indicated for active primary immunization for prevention of invasive disease caused by *Haemophilus influenzae* type b and meningococcal disease caused by *Neisseria meningitidis* serogroups C and Y in infants and toddlers. MenHibrix vaccine is proposed to be administered as a 4-dose series (0.5-mL dose) by intramuscular injection at 2, 4, 6, and 12 through 15 months of age. The first dose may be given as early as 6 weeks of age.

1 page redacted due to (b)(4)

The purified *Neisseria meningitidis* type C polysaccharide herein called MenC, consists -
----- (b)(4) -----
----- . The structure of the *Neisseria meningitidis* group C
polysaccharide is shown in figure 1.

[(b)(4)]

Quality decisions which are made during MenC production are described in the MenC
portion of the submission module 3.2.S.2.4. Quality decisions and attributes are
discussed in the section on QC specifications in this memo.

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

The MenC-TT drug substance and intermediates will be commercially manufactured and tested as outlined below:

Manufacturers	Responsibilities
(b)(4)	(b)(4)
	(b)(4)
	(b)(4)
	(b)(4)
(b)(4)	(b)(4)
	(b)(4)
GlaxoSmithKline Biologicals S.A. 89, rue de l'Institut 1330 Rixensart Belgium	Purified and (b)(4) Tetanus Toxoid manufacture
	Purified and (b)(4) Tetanus Toxoid testing
	Conjugated <i>N. meningitidis</i> group C purified polysaccharide manufacture
	Conjugated <i>N. meningitidis</i> group C purified polysaccharide testing

A detailed description of the manufacturing process is included in the file. Translated blank batch records and related examples of executed batch records are included. The serogroup C polysaccharide used to make the MenC-TT conjugate is a -----(b)(4)----- . The manufacturing process for the serogroup C polysaccharide consists of -----(b)(4)----- .

6 pages redacted due to (b)(4)

_____ :

- GSK states that the specifications have been established to allow the assessment of the safety and of the consistency of manufacture of *N. meningitidis* serogroup C polysaccharides. The specifications the firm applied to most tests are those recommended by the ---b(4)-----. Some release limits have been established using information from the testing of development batches. The limits proposed in the WHO guideline “Requirements for Meningococcal polysaccharide vaccine” (adopted 1975, TRS 594, annex 2) were also taken into consideration. GSK’s justification of specifications for their serogroup C polysaccharide is provided in the table below.

22 pages redacted due to (b)(4)

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

Viral Adventitious agents

Viral safety issues are not a concern in the production of MenHibrix as no viral agents come in contact with any of the materials used in the manufacture of MenHibrix. Furthermore, the machinery used to produce MenHibrix has not been used to grow viral material. The culture media also do not support virus growth.

Excipients

No materials of animal origin are used in the excipients for MenHibrix. Therefore, there should be no TSE concerns arising from excipients.

Manufacture of Drug Substance MenY-TT:

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----- (b)(4) -----
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• -----;
• -----;
• ----- (b)(4) -----;
• -----

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

[(b)(4)]

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

1 page redacted due to (b)(4)

The MenY-TT drug substance and –b(4)----- will be commercially manufactured and tested as outlined below:

Manufacturers	Responsibilities
(b)(4)	(b)(4)
	(b)(4)
	(b)(4)
	(b)(4)
(b)(4)	(b)(4)
	(b)(4)
GlaxoSmithKline Biologicals S.A. 89, rue de l'Institut 1330 Rixensart Belgium	Purified and (b)(4) Tetanus Toxoid manufacture Conjugated <i>N. meningitidis</i> group Y purified polysaccharide manufacture

A detailed description of the manufacturing process is included in the file. Translated blank batch records and related examples of executed batch records are included. The serogroup Y polysaccharide used to make the MenY-TT conjugate is a polymer of -----(b)(4)----- . The manufacturing process for the serogroup Y polysaccharide consists of -----(b)(4)----- .

(b)(4)

(b)(4)

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

4 pages redacted due (b)(4)

Use of and relevant issues are discussed in the MenC section of this memo. This process is discussed in detail in the MenC section of this memo. The processes are identical between the MenC and MenY conjugates.

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

[(b)(4)]

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

[(b)(4)]

5 pages redacted due to (b)(4)

The differences are in the -----(b)(4)----- content tests. In future lots, the tests will be conducted by ---(b)(4)---, instead of by the methods listed in Table 7 above. -----(b)(4)----- were submitted in section 3.2.S.3.1 under structure elucidation. However, GSK provided no SOPs for the ---(b)(4)---.

As discussed in the MenC section of this memo, the firm needs to provide data showing that the same polysaccharide lot shows a positive -----(b)(4)----- and comparative data that shows that (b)(4) clearly establishes the --(b)(4)----- of the polysaccharide

GSK states that the specifications have been established to allow the assessment of the safety and of the consistency of manufacture of *N. meningitidis* serogroup Y polysaccharides. The specifications the firm applied to most tests are those recommended by the -----(b)(4)----- . Some release limits have been established using information from the testing of development batches. The limits proposed in the WHO guideline “Requirements for Meningococcal polysaccharide vaccine” (Adopted 1975, TRS 594, annex 2) were also taken into consideration. GSK’s justification of specifications for their serogroup Y polysaccharide is provided in the table below.

[(b)(4)]

As stated above, these specifications were used for the clinical and commercial consistency lots. However, as described above, these specifications will not all be used for future production lots. The firm instead proposes to revise some of the specifications to be based on (b)(4). The source of these proposed specifications are as follows:

[(b)(4)]

The proposal to change from -----(b)(4)----- for the specifications in Table 4 is acceptable, however, there are specific issues raised with the methods and validation of the (b)(4) assays (see the discussion in the MenC portion of the memo).

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

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

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

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

[(b)(4)]

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

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9 pages redacted due to (b)(4)

Manufacture of Drug Product Hib-MenCY-TT:

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

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

The immediate packaging materials used for the container-closure system are equivalent to those used for other vaccines manufactured by GlaxoSmithKline Biologicals. The final container vaccine is presented as a lyophilized preparation in --- (b)(4) --- glass vials sealed with a rubber closure and flip off caps. Each vial of vaccine is reconstituted with the content of a ---- (b)(4) ----- containing the 0.9% Sodium Chloride diluent. The volume overage facilitates withdrawal of the 0.5 mL dose. The information on saline diluent is provided in the BLA and will be discussed separately.

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)	(b)(4)
Tris (Trometamol)-HCl	96.8 µg		
Diluent			
NaCl			

- Pharmaceutical form: lyophilized product, to be reconstituted with saline diluent before injection
- Presentation: monodose in glass vials
- Administration: intramuscular injection
- Storage: +2°C to +8°C
- Overfill: a formulation overage of approximately is 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:
 - Hib (or PRP) = capsular polysaccharide (Polyribosyl Ribitol Phosphate)
 - TT = Tetanus Toxoid

The Hib-MenCY-TT vaccine contains three polysaccharides, each conjugated to Tetanus toxoid, coded Hib-TT, MenC-TT and MenY-TT. The compatibility of the drug substances with each other was demonstrated in clinical trials. The compatibility between the drug substances and the excipients is supported by the satisfactory real-time stability data generated at the recommended storage temperature as well as by the satisfactory immune response induced against all vaccine antigens.

The following excipients are used in the vaccine:

- Sucrose -----(b)(4)-----,
- Tris-HCl -----(b)(4)-----

1 page redacted due to (b)(4)

Hib-MenCY-TT final container vaccine will be commercially manufactured, tested, and packaged as outlined below:

---(b)(4)----- of Hib-MenCY-TT vaccine is performed by:

GlaxoSmithKline Biologicals SA
89, rue de l'Institut
1330 Rixensart
Belgium

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

-----:

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

-----:

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

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

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

The consistency of the Hib-MenCY-TT vaccine production process was demonstrated through analyses of the process data collected during the manufacture of formulated bulks and finished product, as well as through the analysis of Quality Control data for the release of formulated bulks and finished products.

Each batch of final bulk and finished product is tested according to the GSK Biologicals' specifications as follows:

[(b)(4)]

[(b)(4)]

4 pages redacted due to (b)(4)

Following analytical test development at GSK Bio and following feedback received from CBER under IND No. (b)(4), the QC release testing for the first commercial lots include the following main differences compared to the tests performed on clinical lots:

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

As shown in Table 5, all commercial lots comply with the proposed release specifications. Results of testing demonstrate consistency of commercial production. As shown in Table 6 and Table 7, all clinical lots complied with specifications at time of release.

Additional tests were also performed for (b)(4) (Hib-TT, MenC-TT and MenY-TT), PSY content, --(b)(4)--- content and general safety. All results comply with the proposed specifications and demonstrate consistency between the clinical batches.

Results of tests are comparable for commercial and clinical lots however GSK's results of -----(b)(4)----- for MenC-TT and MenY-TT are slightly lower for commercial lots. The firm explains that this is due to the variability of the method. They performed repeat testing on (b)(4) commercial lots using ----(b)(4)----- . The firm states that the results of repeat testing show values comparable to the data obtained on clinical lots.

However, the firm's explanation for the difference in (b)(4) as caused by a (b)(4) change is inadequate. As follows:

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

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

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

Final Bulk Hold Time Validation

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

(b)(4)

(b)(4)

(1) (1)

1 1 9

(b)(4)

The firm proposes an expiration date of 36 months for final filled drug product. They base this proposed expiration date on data from studies on clinical products and --(b)(4)-- of real-time data with commercial drug product. As described in detail in this review, multiple changes in the manufacturing process occurred between clinical and commercial consistency lots. The firm should provide data for the --(b)(4)-- time point and propose a dating for final drug product that is consistent with actual data obtained for commercial drug product.

Stability testing of reconstituted vaccine

However, the firm does not propose to perform reconstitution studies as part of their routine on-going stability studies. Reconstitution of lyophilized product as part of stability should be performed routinely in the firm's on-going stability studies.

Future stability studies

Stability of the final container commercial lots in support of the BLA was assessed as follows:

[(b)(4)]

The firm proposes to place (b)(4) lot per year of final product on their on-going stability program as described in the table below.

[(b)(4)]

This plan for on-going stability is provided in Section 3.2.P.8.2 (Post-approval Stability Protocol and Stability Commitment Hib-MenCY-TT) of the BLA. The firm has not included -----(b)(4)----- in their proposed protocol. The firm has not provided a rationale for deletion of these assays from their post-approval stability protocol. They need to add these assays back in to their stability protocol for final containers.

Complete Response Items

The firm should address the following in a Complete Response Letter:

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 sterile filtration, the date of filling into final containers or some other measure.
2. We note that you refer to multiple GSK monographs throughout the CMC sections of the BLA, however you have not provided these monographs for review. Please submit all GSK monographs related to CMC of MenHibrix at all manufacturing stages.

Drug Substance

- 3.
- (b)(4)
- 4.
- (b)(4)
- 5.
- (b)(4)

4 pages redacted due to (b)(4)

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

c.

Drug Product

13. In Section 3.2.P.8.3 (Stability Data, Hib-MenCY-TT) you note that the stability results for -----(b)(4)----- show a slight --(b)(4)-- over time. You indicate that in Tables 14 and 15 of this section for (b)(4) MenC-TT and (b)(4) MenY-TT, different (b)(4)-- were used after the ---(b)(4)--- time point. You propose that the variability of the method is mainly due to the variability of the (b)(4) used and that use of a different (b)(4)- at these time-points seems to introduce a bias towards a -----(b)(4)----- of MenC-TT and MenY-TT. Please address the following with respect to the -----(b)(4)-----:
- a. Your explanation that a (b)(4) change is responsible for a --(b)(4)-- in the (b)(4) is inadequate. If the method and --(b)(4)---- were properly validated and qualified, a decrease in (b)(4) should not have been seen as a result of a (b)(4)-- change only. Please clarify.
 - b. As described previously, you provide --(b)(4)-- characterization data which show inconsistencies in the (b)(4) between the commercial and clinical lots. These data demonstrate that the molecular weight of the conjugates can vary widely. Therefore, we do not agree that the --(b)(4)---- may be primarily due do a change in --(b)(4)--. Please comment. Please provide any data for validation of the --(b)(4)-- assay.
 - c. You indicate that from currently available data, a decrease in MW cannot be ruled out. Please provide an explanation for this statement in terms of product stability and consistency.
14. 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 pH and Free PS (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.

15. 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)--- 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.
16. 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.
17. In Amendment 1 dated 8/27/2009 you provide a validation study for determination of -----(b)(4)----- (9000001149RVM002/V1.0). You state in this validation study that “all raw data have been stored in the --(b)(4)--- order available in ----(b)(4)----- We note also that in Amendment 3 dated 2/12/2010 you report a change in contract testing for ----(b)(4)----- to -----(b)(4)----. Please clarify if the validation data in the report were from studies performed at (b)(4) or from studies performed at GSK, and if these studies assessed detection of -----(b)(4)----- in actual Hib-TT, MenC-TT, and MenY-TT bulk conjugate samples. If the studies were not performed at (b)(4), please provide a plan specifying how (b)(4) will perform validation studies for ----(b)(4)----- determination using the (b)(4) bulk conjugates and when you will submit these data for review.
18. In Amendment 3 dated 2/12/2010 you provide revisions to multiple data tables (e.g. stability data values, batch analyses data values, QC test values). Please provide a complete explanation of the source of these errors reported in the data tables. For example, please explain whether these are data transcription errors, calculation errors, or other types of errors. In addition, please describe at what level the error occurred (manufacturing, quality department, preparation of batch records, testing laboratories, etc.) and any related investigations and corrective actions taken as a result of the errors.