



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

Food & Drug Administration
1401 Rockville Pike
Rockville, MD 20852

MEMORANDUM

Date: April 28, 2010

From: Willie F. Vann, Committee Member
Chief, LBP/ 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

Amendments Reviewed:

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

This review memo covers the 0.9% Sodium Chloride diluent used to reconstitute the lyophilized Menhibrix final container vaccine.

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 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 GlaxoSmithKline Biologicals' combined Hib-MenCY-TT conjugate vaccine, is composed of the following three active ingredients: the purified capsular polysaccharides of *Haemophilus influenzae* type b, *Neisseria meningitidis* group C and *Neisseria meningitidis* group Y, each conjugated to tetanus toxoid. These conjugates are coded, respectively: Hib-TT, MenC-TT and MenY-TT.

Review of Diluent

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 immediate packaging materials used for the container-closure system are equivalent to those used for other vaccines manufactured by GlaxoSmithKline Biologicals. The composition of GSK Biologicals' Hib-MenCY-TT vaccine is provided in Table 1, 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)	(b)(4)
Tris (Trometamol)-HCl pH (b)(4)	96.8 µg	(b)(4)	(b)(4)
Diluent			
NaCl	4.5 mg	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)	(b)(4)

Diluent

The 0.9% sodium chloride diluent used to reconstitute Hib-MenCY-TT vaccine is presented in pre-filled glass syringes. The 0.9% sodium Chloride diluent is formulated by -----(b)(4)----- with the appropriate amount of NaCl. NaCl and (b)(4) comply with -----(b)(4)----- respectively. The diluent is manufactured and tested at either:

GlaxoSmithKline Biologicals SA.
 89,Rue de l'Institut
 1330 Rixensart
 Belgium
 or

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

All diluent used to prepare commercial lots were prepared at GSK Rixensart. As described above, the diluent is formulated from NaCl and (b)(4). The bulk diluent is -----
 -----(b)(4)-----
 -----.

The specifications for the diluent are listed below:

Table 1 Specifications for the 0.9% sodium chloride diluent – Final Container

Tests	Specifications
Description of the liquid	(b)(4)
(b)(4)	
Volume	
Sterility test (b)(4)	
Sterility test (b)(4)	
(b)(4)	
Identity sodium	
Identity chlorides	
Sodium chloride content	
(b)(4)	

The specifications are the same for diluent produced at both sites. Diluent produced at ---
 -----(b)(4)----- by GSK at Rixensart. The diluent assays are by compendial methods. There are no adventitious agents or suspected toxins present in the diluent based on submitted data.

The batch analysis in support of the diluent manufacturing process was satisfactory. The data are given in the tables below. The firm reported a -----(b)(4)----- for the diluent. The -----(b)(4)----- did not have an adverse effect on the diluent.

1 Page Determined to be Not Releasable: (b)(4)

(b)(4)



Comment: The date of manufacturing of the diluent should be clearly defined.

Stability of the Diluent

---(b)(4)--- stability data are available for lots produced at GSK by the current process with -----(b)(4)-----) when stored at -----(b)(4)----- months stability data are available for lots -----(b)(4)----- using the -----(b)(4)----- stored at ----(b)(4)-----C. All lots meet specifications. The stability study is ongoing.

---(b)(4)-- stability data are available for lots manufactured using the ---(b)(4)--- filtration procedure for sterilization and a ---(b)(4)-- stopper from all of the lots above (----- (b)(4)-----). The firm is requesting --(b)(4)- expiration dating of diluent at -----(b)(4)-----.

Comment: My recommendation is ---(b)(4)--- at -----(b)(4)-----based on available data with the current sterilization process.

The stability plan for the diluent using the current process and stopper is outlined below.

Table 1 Stability protocol for 0.9% sodium chloride diluent in (b)(4) at (b)(4)

Tests	(b)(4)
Description	(b)(4)
(b)(4)	(b)(4)
Volume	(b)(4)
Sterility test	(b)(4)
Sterility test	(b)(4)
(b)(4)	(b)(4)
Identity chlorides	(b)(4)
Identity sodium	(b)(4)
Sodium chloride content	(b)(4)
Container closure integrity	(b)(4)

For future commercial lots, GSK commits to place ---(b)(4)--- per year to be followed for real time stability in accordance with the following stability plan:

Table 2 Stability protocol for 0.9% sodium chloride diluent in (b)(4) per filling year (b)(4)

Tests	(b)(4)
Description	(b)(4)
Sterility test	(b)(4)
Sterility test	(b)(4)
Sodium chloride content	(b)(4)
(b)(4)	(b)(4)
Container closure integrity	(b)(4)

GSK has made several changes to their proposed on-going stability protocol for diluent but has not provided a rationale for these changes. Specifically, GSK made the following changes:

- The stability studies in support of the BLA were performed at ---(b)(4)---. However, stability studies for future lots will be performed at -(b)(4)--
- The testing plan for the future lots does not include volume, particle count, chloride identity, or sodium identity

Comment: The firm should provide a rationale for the changes in their on-going stability program for diluent.

Complete Response Items

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

1. Please provide information specifying how the date of manufacture is determined with respect to the expiration dating period for the 0.9% Sodium Chloride diluent used to reconstitute Menhibrix vaccine. 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. You propose a (b)(4) month expiration date for the 0.9% Sodium Chloride diluent based on stability collected with a –(b)(4)-- plunger stopper and ---(b)(4)--- sterilization process than 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.
3. 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)-----, and volume, particle count, chloride identity, and sodium identity have been deleted from the protocol. Please provide a rationale for these proposed changes.