



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

To: 125363/0

From: Sean Byrd, Dir. Reg. Rev. Ofc., CBER/OCBQ/DMPQ/BI, HFM-675

Through: Carolyn Renshaw, Chief, CBER/OCBQ/DMPQ/BI, HFM-675

Applicant: GlaxoSmithKline Biologicals, License #1617

Product: Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine [MenHibrix®]

Subject: Review Memo – Original Application for Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine.

RECOMMENDATIONS:

Based on all submitted information I recommend approval of GlaxoSmithKline Biologicals Biologics License Application (STN 125363/0). This recommendation is based partially on the adequacy of information found in the amendment sequence #21 (the content of this memo), and my review of the CBER DMF-(b)(4) (attached) as well as all other review memos found in the Electronic Document Room.

BACKGROUND

GlaxoSmithKline Biologicals submitted a BLA on 12 August 2009. It has gone through several amendments, the latest of which submitted on 30 November 2011, is for 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) CBER DMF-(b)(4) in support of the change. Note that the DMF was originally reviewed in support of the identical change to GSKs product, *Hiberix* (STN: 125347/(b)(4), 9 March 2012).

The diluent is manufactured by -----(b)(4)-----

The 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, STN 103239/5268. (----- (b)(4) -----)

MenHibrix® is a lyophilized vaccine to be reconstituted with supplied diluent at time of use.

GSK States this amendment is submitted to introduce 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 provides the following in support:

- Letters of Authorization to reference ----- (b)(4) ----- and to reference container-closure Drug Master Files.

COMMENT: Only DMF-(b)(4)- and the GSK amendment were reviewed. Sufficient information is provided in these two documents to support approval. The additional CBER referenced DMFs are ---- (b)(4) ---- for facilities, utilities, equipment, operations and products at ----- (b)(4) ---- for rubber stoppers by (b)(4) (these stoppers were approved for use with vials with (b)(4) necks on 25 May 2007 by ----- (b)(4) -----). CDER --- (b)(4) --- for the vials was not reviewed.

- Modules 2 and 3 of the eCTD sections to include:
 - 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;
 - 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.

REVIEW

Product Description

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 3 mL ----- (b)(4)- glass vials closed with an elastomeric stopper, and sealed with an -- (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 quantitative composition is shown in the table below.

Table 1 Composition of the 0.9 % Sodium Chloride Diluent Solution

Ingredient	Quantity per Vial	Function	Reference to Standards
Sodium chloride	(b)(4)		

Manufacturing process

Please refer to my (Sean Byrd) review of the CBER DMF-(b)(4) for this information. The review was completed on 8 March 2012 and can be found in BIRAMS as well as attached to this review memo.

Facilities and Equipment

Please refer to my (Sean Byrd) review of the CBER DMF--(b)(4)-- for this information. The review was completed on 8 March 2012 and can be found in BIRAMS as well as attached to this review memo.

Stability

The chart below shows the current protocol for stability testing of the validation lots.

(b)(4)

The table below describes tests and acceptance criteria proposed for the commercial stability protocol for storage at (b)(4) at (b)(4) and (b)(4) at GSK.

Test	Test Method (SOP#)	Acceptance Criteria
Sterility	(b)(4)	
Visual Appearance		
pH		
Sodium Chloride Assay		
Container Closure Integrity		
1. (b)(4)	performs this testing	(b)(4)
2. GSK	performs the container closure integrity test at	(b)(4) storage conditions

The submission provides (b)(4) months stability for validation lots -----(b)(4)-----, and -----(b)(4)----- . It also contains a revised (b)(4) month report for lot ---(b)(4)--- for storage at (b)(4). Along with the acceptance criteria described above, GSK states it also includes --(b)(4)- for particulate matter. Each batch was a total of (b)(4) and were manufactured and filled on -----(b)(4)-----, 2011 respectively.

The data provided concerning visual appearance, sterility, pH, endotoxin, CCIT, and particulates appear to indicate the diluent remains stable under the conditions described and the containers remain integral. All deviations appear to have been minor (late testing after the first 4 weeks, malfunctioning --(b)(4)--) and were adequately addressed. Note that Visual Appearance is a 100% visual inspection for defined Critical, Major, and Minor defects to include particulates. The process is performed using a -----(b)(4)----- following (b)(4) approved procedures.

GSK also provides a Post Approval stability commitment where a minimum of (b)(4) commercial lot will be placed on long-term stability each year, if manufactured. The data provided will be in support of a --(b)(4)-- expiry date.

Container Closure Integrity Test

The protocol 9000001067 noted above in blue and described in this submission is the same in 125347/(b)(4) and is validated. The validation covered syringe and --(b)(4)-- vial presentations. Acceptance criteria were met.

Container Closure/Primary Packaging Materials

Please refer to my (Sean Byrd) review of the CBER DMF-(b)(4) for this information. The review was completed on 8 March 2012 and can be found in BIRAMS as well as attached to this review memo.

Equipment Qualification

Please refer to my (Sean Byrd) review of the CBER DMF-(b)(4) for this information. The review was completed on 8 March 2012 and can be found in BIRAMS as well as attached to this review memo.

REVIEWER COMMENT:

The review of the DMF was performed for the product *Hiberix*. This is acceptable as there are no differences in diluent between *Hiberix* and *Menhibrix*.