Summary Basis for Regulatory Action

Date	14 June 2012
From	Joseph J. Temenak, Ph.D., Chair
BLA/STN#	125363/0
Applicant Name	GlaxoSmithKline Biologicals
Date of Submission	12 August 2009
PDUFA Goal Date	31 August 2012
Proprietary Name / Established Name	MenHibrix / Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine
Proposed Indication	Active immunization for the prevention of invasive disease caused by *Neisseria meningitidis* serogroups C and Y and *Haemophilus influenzae* type b. MenHibrix is approved for use in children 6 weeks of age through 18 months of age.
Dosage Forms	Solution for injection supplied as a single-dose vial of lyophilized vaccine to be reconstituted with the accompanying vial of saline diluent. A single dose, after reconstitution, is 0.5 mL.
Recommended Action	Approval
Signatory Authorities Action: Office Signatory Authority	 Marion F. Gruber, Ph.D. Director, Office of Vaccines Research and Review

X I concur with the summary review.

☐ I concur with the summary review and include a separate review to add further analysis.

☐ I do not concur with the summary review and include a separate review.

Table 1: Review documents used in compiling this SBR**A**

Review Category	**Reviewer--date of review**
Clinical Review	Meghan Ferris, M.D. – 3 June 2010, 14 June 2012
Statistical Review	Barbara Krasnicka, Ph.D. – 28 May 2010, 24 April 2012
Statistical Assay Review	Tsai-Lien Lin, Ph.D. – 26 May 2010, 1 September 2011, 13 April 2012
Pharmacovigilance Review	Trish Rohan, M.D. -- 7 May 2010 Manette Nui, M.D. – 25 April 2012
CMC Review	Mustafa Akkoyunlu, M.D., Ph.D. – 5 May 2010, 13 August 2011, 16 April 2012 Willie Vann, Ph.D. – 4 May 2010 Daron Freedberg, Ph.D., 5 May 2010, 13 September 2011, 16 April 2012, 2 May 2012 Drusilla Burns, Ph.D. – 15 March 2010 Michael Schmitt, Ph.D. – 21 April 2010, 1 September 2011, 15 May 2012 Freyja Lynn, Ph.D., -- 19 January, 2012, 27 March 2012 (2 reviews) James Keller, Ph.D. – 4 May 2010, 29 August 2011, 14 May 2012 Tina Roecklein – 10 May 2010, 25 August 2011, 12 June 2012
Division of Biological Standards and Quality Control (DBSQC) -Lot testing	Rajesh Gupta, PhD - 29 August 2011, 6 September 2011, 23 April 2012 Karen Campbell – 5 June 2012, 13 June 2012 Manju Joshi – 06 May 2012 James Kenney, Ph.D. – 23 May 2012 Alfred Del Grosso, Ph.D. – 30 May 2012
Assays (concomitant)	Annisa Cheung –22 January 2010 Majiid Laassri, Ph.D. – 29 January 2010 Steven Rubin, Ph.D. – 8 January 2010 Shuang Tang, Ph.D. – 14 May 2010, 18 July 2011 Iryna Zubkova, Ph.D. – 11 April 2010 Steve Feinstone, Ph.D. – 17 May 2010
Facilities Review	Sean Byrd – 27 May 2010, 29 July 2011, 25 October 2011, 2 May 2012, 17 May 2012, 14 June 2012 (2 reviews) Joseph George - 28 May 2012
Bioresearch Monitoring Review	Robert Wesley – 26 January 2010 Solomon Yimam – 13 May 2010
Consult Review – Extractable/Leachables	Rabia Ballica, Ph.D. – 18 May 2012
Establishment Inspection Report	Joseph George and Willie Vann, Ph.D. – 2 December 2010
Pharmacology/Toxicology Review	Steve Kunder, Ph.D. – 6 May 2010
Container and Labeling	Maryann Gallagher – 20 October 2009, 20 October 2009 (2 reviews same date), 30 March 2012, Daphne Stewart – 23 October 2010
Proprietary name review	Maryann Gallagher – 20 March 2012, 10 April 2012

1. Introduction

On 12 August 2009 GlaxoSmithKline Biologicals, Rixensart, Belgium (US License 1617) submitted a biologics license application (BLA) for Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine. The proprietary name MenHibrix is proposed for the candidate vaccine. MenHibrix contains no preservative, and when reconstituted, is a solution for intramuscular injection (0.5 mL dose). It is supplied in a carton containing 10 single-use vials of lyophilized vaccine to be reconstituted with the accompanying 10 single-vials of saline diluent prior to intramuscular injection of the 0.5 mL dose. MenHibrix is intended for active immunization for the prevention of invasive disease caused by *H. influenzae* type b and *N. meningitidis* serogroups C and Y. The indicated age range for use is 6 weeks through 18 months of age. MenHibrix is administered as a four dose series at 2, 4, 6 and 12-15 months of age.

2. Background

MenHibrix is a vaccine that contains as active ingredient capsular polysaccharide (polyribosyl-ribitol-phosphate, PRP) prepared from a strain of *H. influenzae* type b and capsular polysaccharides C and Y prepared from *N. meningitidis* serogroups C and Y (PSC and PSY, respectively), with each of the 3 polysaccharides covalently bound to tetanus toxoid (TT). Each 0.5 mL single dose of MenHibrix is formulated to contain 2.5 mcg of purified PRP covalently bound to 6.25 mcg TT, 5 mcg PSC covalently bound to 5 mcg TT, and 5 mcg PSY covalently bound to 6.5 mcg of TT.

Currently, there are no other US licensed manufacturers of this particular combination product, and there is currently no US licensed meningococcal conjugate vaccine for use in young infants. Other manufacturers of licensed Haemophilus b Conjugate Vaccines in the U.S. include Merck & Co., Inc., which produces PedvaxHIB [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)] and COMVAX [Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine], and Sanofi Pasteur which produces ActHIB [Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)], TriHIBit [ActHIB reconstituted with Tripedia (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed)], and Pentacel [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine]. GSK produces Hiberix [Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)]. All of these vaccines are approved for primary and booster immunization against invasive disease due to *H. influenzae* type b, with the exception of TriHIBit and Hiberix, which are approved for booster immunization only. Novartis produces Menveo [Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine] for use in individuals 2 through 55 years of age. Sanofi-Pasteur produces Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine], which is licensed for use in children as young as 9 months of age. Sanofi-Pasteur also produces Menomune-A/C/Y/W-135 [Meningococcal Polysaccharide Vaccine (Groups A, C, Y and W-135)], which is licensed for use in individuals 2 years of age and older.

Due to technical concerns regarding the serum bactericidal assay using human complement that forms the basis for evaluation of meningococcal Y immunogenicity (hSBA-MenY) and inference to the

effectiveness of the Y component CBER previously issued two Complete Response (CR) letters. The CR letters also included comments related to chemistry, manufacturing, and controls (CMC). The applicant provided a response to these letters in submissions dated April 15, 2011 and December 1, 2011. In a submission dated 27 March 2012, the applicant completely addressed all of CBER's remaining concerns regarding the assays and CMC.

3. Chemistry Manufacturing and Controls (CMC)

General Manufacturing Summary

MenHibrix is a 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 (TT), and lyophilized in the presence of sucrose and Tris-HCl. The formulation of Hib-MenCY-TT is performed at the GSK site in Rixensart, Belgium. Filling and lyophilization are performed at the GSK site in –b(4)----------. Labeling and primary packaging of the lyophilized MenHibrix vaccine is performed by GSK at the -----b(4)------ site. The vaccine is reconstituted with 0.6 mL of 0.9 % saline diluent provided by --------b(4)----------. Manufacture (---b(4)----------) and primary labeling and packaging) of the 0.9% NaCl diluent is performed by –b(4)---------- site. The GSK ---b(4)---------- site also conducts container closure integrity testing of the diluent. The final labeling and packaging (kitting) of MenHibrix vaccine (a carton containing 10 vials of vaccine) with the packaged diluent (a carton containing 10 vials diluent) into one combination package is performed at the GSK site in -------b(4)----------

Drug Substance

MenHibrix vaccine is composed of three drug substances (Hib-TT, MenC-TT, and MenY-TT). The Hib-TT drug substance of MenHibrix consists of the capsular polysaccharide from *Haemophilus influenzae* type b covalently bound to tetanus toxoid (carrier protein). Haemophilus type b polysaccharide consists of a repeating polymer of D-ribosyl and ribitol phosphate linked through a b(4) linkage. The Hib-TT drug substance will be commercially manufactured at the following locations: GSK (--b(4)----------), GSK (Rixensart, Belgium), and GSK (---b(4)----------). The Hib-TT manufacturing process consists of the following main steps: ----b(4)----------. For the Hib-TT conjugate, the polysaccharide to protein ratio (PS/TT) by calculation is between –b(4)----------. A detailed description of the manufacturing process is included in the file. The MenC-TT and MenY-TT drug substances of MenHibrix consists of the *Neisseria meningitidis* serogroup C or Y capsular polysaccharide, respectively, covalently bound to tetanus toxoid. For the MenC-TT conjugate, the ratio of PS/TT conjugate is between ---b(4)-----, and for the MenY-TT conjugate is between ---b(4)---. The MenC-TT and MenY-TT drug substances will be commercially manufactured at the following locations: GSK ----b(4)---------- GSK (Rixensart, Belgium), and GSK ---b(4)---------- For both MenC-TT and MenY-TT the manufacturing

processes consist of the following main steps----b(4)----------
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---------- Detailed descriptions of the manufacturing processes are included in the file.

There are multiple in-process (quality decision and monitoring) tests performed at each step of the Hib-TT, MenC-TT, and MenY-TT manufacturing processes. The purified Men C and MenY polysaccharides, purified TT, and –b(4)---------- Men C and MenY are considered --b(4)----------. The QC release specifications for the Hib-TT, MenC-TT, and MenY-TT drug substances are all outlined in the license application. The specifications applied by GSK to most of the tests are those recommended by ----b(4)----------and WHO Technical Report Series 897. When appropriate, release limits have been established based on batch analysis data. Analytical procedures and validation reports for Hib-TT, MenC-TT, and MenY-TT were found to be acceptable.

GSK included data in the BLA to demonstrate consistency of manufacturing and determined critical operating parameters as part of their process validation. Details on validation of the manufacturing process for the drug substances are described in Mr. Joseph George's review memorandum of 9 June 2010. Refer to Ms. Tina Roecklein's review memorandums dated 4 May 2010, 25 August 2011, and 12 June 2012 for additional details on Hib-TT, MenC-TT, and MenY-TT drug substance specifications, and to Dr. Daron Freedberg's reviews of 05 May 2010 and 2 May 2012 for additional details on MenC-TT drug substance and MenY-TT drug substance specifications.

Drug Product

The components of the MenHibrix vaccine and the 0.9 % NaCl diluent solution are as listed in Tables 1 & 2 below:

Table 1. Composition of MenHibrix Vaccine

Ingredients	**Quantity (per dose 0.5 mL)**
Conjugate of *Haemophilus influenzae* type b capsular polysaccharide and tetanus toxoid (mean TT/PS ratio: 2.5)	2.5 µg Hib 6.25 µg TT
Conjugate of *Neisseria meningitidis* C capsular polysaccharide and tetanus toxoid (mean TT/PS ratio: 1)	5 µg MenC 5 µg TT
Conjugate of *Neisseria meningitidis* Y capsular polysaccharide and tetanus toxoid (mean TT/PS ratio: 1.3)	5 µg MenY 6.5 µg TT
Sucrose	12.6 mg
Tris (Trometamol)-HCl pH –b(4)-	96.8 µg
Sodium Chloride	--b(4)--
---------b(4)----------	----b(4)---------

- Pharmaceutical form: lyophilized product to be reconstituted with saline diluent prior to injection
- Presentation: lyophilized monodose in ---b(4)------glass vials for reconstitution with 0.6 mL saline.
- Storage: +2ºC to +8ºC
- Overfill: a formulation overage of approximately b(4) is applied in order to guarantee an injectable dose of 0.5 mL containing 2.5 µg of Hib, 5 µg of each MenC and MenY polysaccharides.

Table 2. Composition of the 0.9 % Sodium Chloride Diluent Solution

Ingredients	Quantity per Vial (0.85 mL)
Sodium chloride	--b(4)---
-----b(4)----------	---b(4)-------

- Presentation: --b(4)--- glass vials sealed with a rubber stopper
- Storage: +2ºC to +25ºC
- Overage: The target fill volume of 0.85 mL is sufficient to ensure that 0.6 mL can be withdrawn for reconstitution of the lyophilized vaccine. No overage is present in the strength of the 0.9% saline solution. However, a volume of 0.85 mL is provided in each vial to allow for extraction of 0.6 mL needed for reconstitution of the lyophilized vaccine.

The formulation of MenHibrix Final Drug Product is performed by –b(4)-- sterile solutions of sucrose and Tris-HCl buffer with –b(4)---------- and by subsequently adding the appropriate amount of Hib-TT, MenC-TT and MenY-TT conjugate bulks. The final bulk is aseptically filled into –b(4)------ ----------. Throughout this process, assembled vials are visually inspected for the aspect of the cake, defects in the vial and conformity of the closure system. Non-conforming containers are rejected, accounted for and discarded. Lyophilized vials are sealed with –b(4)---- flip-off caps.

The ingredients in the drug product other than the active substance are sucrose, Tris-HCl, and NaCl, which are tested according to the current ----------b(4)----------.

Control of Drug Product:

Specifications for release of MenHibrix final bulk and final container vaccine are detailed in the Table 3. Final specifications were established using information from the testing of development and commercial batches and through communications between CBER and GSK.

Table 3. Specifications Hib-MenCY-TT Final Bulk

Test	Specifications
----------b(4)----------	----------b(4)----------
----------b(4)----------	----------b(4)----------
----------b(4)----------	----------b(4)----------

Table 4: Specifications Hib-MenCY-TT Final Container

Test	Specifications
Description	White cake or powder, clear and colorless solution after reconstitution with diluent
Identity Meningococcal C conjugate by ELISA	--b(4)------

Identity Meningococcal Y conjugate by ELISA	--b(4)-----
Identity Hib conjugate by –b(4)----	----------b(4)----------
Sterility test ----------b(4)----------	----------b(4)----------
Sterility test ----------b(4)----------	----------b(4)----------
Endotoxin content by ----------b(4)----------	----------b(4)----------
Water content by ---b(4)----------	----------b(4)----------
-b(4)----	----------b(4)----------
Hib content by---b(4)----	----------b(4)----------
Total PSC-PSY content by –b(4)-----	----------b(4)----------
PSY content by –b(4)---	----------b(4)----------
PSC content by calculation	----------b(4)----------
-b(4)- Hib-TT by ----------b(4)----------	----------b(4)----------
-b(4)--- MenC-TT by ----------b(4)------	----------b(4)----------
-b(4)-- MenY-TT by ----------b(4)-------	----------b(4)----------
Water Content by ------b(4)----------	----------b(4)----------
Sucrose content by—b(4)----	----------b(4)----------
---b(4)----------	----------b(4)----------
Endotoxin content by ----------b(4)----------	----------b(4)----------
Sterility test ----------b(4)----------	----------b(4)----------
Sterility test ----------b(4)----------	----------b(4)----------
---------- ----------b(4)------	----------b(4)----------
General safety	----------b(4)----------
General safety	----------b(4)----------

Specifications for release of the –b(4)----- are detailed in the Table 5. Final specifications were established using information from testing and development for test methods, and per b(4) monographs.

Table 5: Specifications –b(4)------- Final Container

Parameter	Test Method	Specification
Appearance	------b(4)---------- ----------	----------b(4)---------- ---------- ---------- ----------
Deliverable Volume	--- –b(4)-	--b(4)-----
-b(4)-	----b(4)---------- -------- ---–b(4)-	--b(4)-----
Identification – Sodium	----–b(4)-	-----b(4)----------

Identification – Chloride	--- –b(4)--	----b(4)---------- ---------- ---------- ---------- ---------- ---------- ---
Sodium Chloride Assay	---b(4)---------- ----------	----------b(4)---------- -
---b(4)----------	---–b(4)-----	--b(4)------
--b(4)-------	----–b(4)----	--b(4)-------

Batch analysis results for MenHibrix are presented in the BLA file. –b(4)----- commercial lots (--b(4)----------) were evaluated and are fully representative of the manufacturing process for US commercial product. Additional batch analyses were included in the BLA. These batches are representative of the manufacturing process proposed for US commercial product. All results met specifications for all batches.

Date of Manufacture:

GSK proposed the start date of filling into final containers as the date of manufacture for MenHibrix Final Container, and the date of manufacture for the diluent to be defined as the start date for filling into final containers. CBER concurs with both of these proposals.

Stability:

MenHibrix vaccine stability was assessed by long-term, real-time stability studies, accelerated stability studies and studies after reconstitution of the vaccine with the saline diluent. Stability data were generated for lyophilized MenHibrix final container that support 36 months of storage at 2-8^{o}C from the date of manufacture. Lyophilized MenHibrix final container vaccine lots were also included in accelerated stability studies at ----b(4)----------. All lots met the specifications.

In addition, stability was assessed following reconstitution of lyophilized vaccine which had been stored for –b(4)--------. The stored vaccine was reconstituted with saline diluent and stability was assessed at time -b(4)- and at –b(4)-- after storage at –b(4)-. At time b(4), all lots met specifications. At –b(4)-, all tests met their specifications with the exception of results obtained for total PSC/PSY content and PSY content tests. Therefore, we asked GSK to label the use of MenHibrix as "use immediately following reconstitution".

GSK commits to place b(4) lot of lyophilized Hib-MenCY-TT per year to be followed for real-time stability according to their current stability plan.

The 0.9% sodium chloride diluent is manufactured, filled, labeled, and packaged by ----b(4)---------- ---------- as described under DMF –b(4)-, and in a GSK supplement to their BLA for Hiberix

(STN 125347/b(4)). The diluent for vaccine reconstitution is filled in –b(4)-------- glass vials fitted with –b(4)- gray butyl rubber stoppers and –b(4)---- crimp seal closure system. Each vial contains 0.85 mL diluent. A 24-month shelf life from the date of manufacture was proposed for the 0.9% sodium chloride diluent to be used for MenHibrix vaccine reconstitution. ---b(4)---------- will be submitted as a future PAS. Stability data to support storage of the diluent at 2-8°C and 20-25°C were provided. GSK proposed to indicate in the product labeling that the storage condition of the diluent is at a controlled temperature from 2-25°C, and CBER agreed with this description for labeling. The CBER reviewer concurs with the proposed 24 month expiry of diluent when stored at 2-25°C. The diluent is labeled and packaged at the –b(4)---------- site and sent to the GSK –b(4)---------- for container closure testing. The final packaging of 10 vials of diluent in a carton is sent from ---b(4)---------- to the GSK –b(4)------ for kitting with the MenHibrix vaccine into a combination box.

---b(4)---------- commits to place b(4) commercial lot of diluent per year on stability at the 25°C storage temperature , provided at least b(4) lot was manufactured that year.

Lot Release

The firm submitted three lots of final drug product in support of approval, AHCYA001C, AHCYA002A, and AHCYA003C. The three lots were tested by CBER for:

- Identity;
- endotoxin (LAL);
- Hib Polysaccharide by HPAEC-PAD (HPLC)
- MenC and MenY Saccharides by HPLC-Fluorescence
- Residual Moisture by Karl Fischer

Additional testing was performed by CBER on two additional lots of final drug product, AHCYA008A and AHCYA008B:

- Total Protein by Lowry colorimetry
- Molecular Size Distribution (MSD) HIB-TT by HPLC-ELISA
- Molecular Size Distribution (MSD) MenC-TT and MenY-TT by HPLC ELISA
- Hib Polysaccharide by HPAEC-PAD (HPLC)
- Residual Moisture by Karl Fischer

The firm also submitted conjugate bulk lots in support of licensure:

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

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All bulk conjugate and final container lots tested were within specifications.

For routine lot release, the firm will submit samples and a Lot Release Protocol for each final container lot to CBER.

A testing plan was developed by DBSQC and approved by the review committee.

General Safety Testing (GST)

The GST will be performed by GSK for each lot of MenHibrix final container vaccine as part of the Lot Release Plan (LRP). GSK submitted a request for exemption from the US GST in accordance with 21 CFR 610.11 in the BLA. CBER denied the request and stated that an exemption from the GST will require demonstrating that multiple lots of product will reliably pass the test. CBER requested that GSK submit a prior approval supplement containing GST data from b(4) lots with their request for an exemption from future testing.

Clinical Serology Assays

The immune response to the meningococcal C (MenC) and Y (MenY) components of MenHibrix was evaluated using a Serum Bactericidal Assay (hSBA). The hSBA assay measures viable meningococci that remain after post-vaccination sera are ----b(4)----------. The reported titer is the serum dilution at which –b(4)- of the bacteria are killed.

The immune response to the Hib component of MenHibrix and control vaccines was evaluated using the *Haemophilus influenzae* polyribosylribitol phosphate (PRP) ELISA. The PRP ELISA assay measures serum –b(4)---------- antibodies against the vaccine antigen. ----b(4)----------. The readout is the concentration of anti-PRP antibody.

In addition, the following clinical assays were used in the BLA to measure response to other vaccines given concomitantly with MenHibrix: ----b(4)---------- was used for Influenza vaccine response; -b(4)---------- and in-house (GSK) assays were used for Hepatitis B vaccine response; --b(4)---------- assay was used for anti-poliovirus 1, 2 and 3 antibodies; --b(4)---------- kits was used for anti-measles, anti-rubella, and anti-mumps antibodies, while an in house –b(4)---------- was utilized for Varicella; An –b(4)-- was used for total pneumococcal IgG antibodies to *Streptococcus pneumoniae*, and –b(4)-- assays were used to measure: 1) antibodies against diphtheria toxoid, 2) antibodies against tetanus toxoid, and 3) anti-PT , anti-FHA, and anti-pertactin (for pertussis) antibodies.

The serological assays were deemed to be adequately validated for their purpose.

Facilities Review

A Pre-License Inspection (PLI) was conducted at GSK's Tetanus Toxoid facility in ---b(4)---------- in March 2010. This inspection was designated VAI and details can be found in the EIR and 483 response review memo. No issues were found that would impact the approvability of the file. The inspection of GSK's Belgium facilities in –b(4)------- and Rixensart, Belgium were waived as per the recommendation of the facilities reviewer (Mr. Sean Byrd) and based on criteria outlined in Center-wide SOPP 8410 "Determining when Pre-License/Pre-Approval Inspections (PLI/PAI) are Necessary."

The data, procedures, and validation studies provided in the application are satisfactory to conclude that the firm has provided the requisite information to support approval.

The packaging and labeling to be used at the GSK –b(4)---- facility were provided in amendments submitted to the BLA on 30 November 2011, 4 June 2012, and 12 June 2012. It was reviewed and found to be acceptable by Mr. Sean Byrd in his review dated 23 April 2012. In addition, the CMC

product reviewer, Ms. Tina Roecklein, reviewed GSK's response dated 12 June 2012 and found it acceptable.

Environmental Assessment

GSK applied for a waiver of an environmental analysis based on the categorical exclusion as described under 21 CFR 25.31(c), which applies to products containing substances that occur naturally in the environment, provided the introduction of these products does not significantly alter the concentration or distribution of the substances, their metabolites, or degradation products in the environment. Based on justification provided in Section 1.12.14 of the BLA, the request for the waiver was found to be acceptable. This assessment is also documented in the Environmental Analysis Assessment review memorandum dated 16 May 2012 by Sean Byrd.

4. Non-clinical/Toxicology

Pre-clinical toxicity studies have been conducted in order to identify and evaluate any toxicity findings following intramuscular (IM) administration of the GSK Biologicals' MenHibrix vaccine. The toxicological profile of the Hib-MenCY-TT vaccine has been studied in two GLP-compliant studies, the results of which were reviewed by Dr. Steve Kunder (review dated 6 May 2010). These studies included a local tolerance/single dose toxicity study in the ---b(4)---------- rabbit and a repeated-dose toxicity study in the –b(4)---------- rabbit. Each of these studies evaluated two formulations of the vaccine: (i) a formulation adsorbed on –b(4)------- phosphate (Hib-ads MenCY ads); and (ii) a non-adsorbed formulation (Hib non-ads MenCY non-ads). The latter formulation was selected for further evaluation of the candidate vaccine in the clinic. The content of each component administered I.M. to rabbits (10 micrograms each) in the toxicity studies was two to four times higher than in the MenHibrix vaccine (2.5/5/5 micrograms). Furthermore, the number of injections given to rabbits (n = 5) in the repeated-dose study exceeded the intended number of injections to be given to infants (n = 4). Data on the toxicity, mutagenicity and sensitization potential of ----b(4)---------- ---------- a byproduct of the reaction used to conjugate the purified polysaccharides of *Neisseria meningitidis* types C and Y to the tetanus toxoid carrier, can be found in Dr. Steve Kunder's review dated 6 May 2010. In summary, toxicity studies have demonstrated that acute intramuscular injection using two to four-fold higher than the human dose produced no toxicologically significant findings in rabbits.

5. **Clinical Pharmacology**

Neisseria meningitidis: The polysaccharide capsule is a principle virulence factor responsible for the pathogenicity of *N. meningitidis*. The primary mechanism by which individuals are protected against invasive meningococcal disease is by antibody-dependent complement-mediated killing. Menhibrix induces antibodies directed against capsular polysaccharides of serogroups C and Y that are bactericidal, and can be measured by human complement assay that detects bactericidal activity in serum.

Haemophilus influenzae type b (Hib): Antibodies to PRP (anti-PRP) have been shown to correlate with protection against invasive Hib disease. MenHibrix induces production of anti-PRP antibodies.

6. Clinical/ Statistical-Efficacy
Summary of Clinical studies

Six clinical studies were included in the BLA. Clinical efficacy endpoint trials were not performed as part of the clinical development program, because they would be difficult to conduct due to low incidence and sporadic occurrence of cases of disease in the U.S. Assessment of effectiveness was based on immunogenicity as assessed in reliable assays. The relevant assays were adequately validated for this purpose (see "Clinical Serology Assays", above). See below for discussion of the immunologic measures used to infer clinical efficacy. Studies with objectives to evaluate the safety and immunogenicity of a 4-dose series of MenHibrix were designated with separate study numbers (i.e., MenHibrix doses 1-3 [Hib-MenCY-TT -009, -007, -005 and -011], followed by a 4th MenHibrix dose in subjects who were enrolled in the studies of doses 1-3 [Hib-MenCY-TT -010, -008,-006, and -012, respectively]). Across the clinical studies, the age range of subjects enrolled was 2 – 6 months for doses 1 – 3, 12 – 18 months for dose 4, and 11 – 36 months for antibody persistence. Pivotal immunogenicity data was based on study Hib-MenCY-TT-009/-010.

Clinical Studies Effectiveness Data

The evaluation of effectiveness of the Hib component of MenHibrix was based on a comparison of the anti-PRP immune response to MenHibrix with the anti-PRP immune response to a U.S. licensed *H. influenzae* type b vaccine, using widely accepted serological correlates of protection against invasive disease due to *H. influenzae* type b. Based on an efficacy study with an unconjugated Haemophilus b polysaccharide vaccine and data from passive antibody studies, an anti-PRP level of 0.15 mcg/mL has been accepted as a minimum protective level. An anti-PRP level of 1.0 mcg/mL has been accepted as predicting long-term (at least one year) protection.

Evaluation of the effectiveness of the meningococcal C and Y components in MenHibrix was based on serogroup-specific bactericidal antibody responses using hSBA. Data from Goldschneider[1], demonstrated that an intrinsic human complement-based Serum Bactericidal Activity (hSBA) assay titer of $\geq$ 1:4 was associated with protection from meningococcal serogroup C. Clinical studies in adults of polysaccharide vaccines demonstrated protection from invasive meningococcal disease caused by serogroups A and C. A determination of effectiveness of polysaccharide vaccines containing serogroups Y and W-135 was based on SBA titers for serogroups Y and W-135 that were similar to SBA titers directed against serogroup C, for which clinical efficacy had been demonstrated. Licensure of meningococcal conjugate vaccine for use in individuals older than 2 years of age was based on SBA titers that are non-inferior to responses observed for other previously licensed meningococcal vaccines (either polysaccharide or conjugate vaccines). For children under age 2 years, use of bactericidal antibody as measured by hSBA was discussed at a meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) in 2011, and CBER was advised

that hSBA would be acceptable to infer effectiveness in this population[2]. Due to the characteristics of the applicant's hSBA assays, a threshold titer of ≥ 1:8 was utilized as the criterion for demonstration of effectiveness following administration of MenHibrix.

Across six studies (Hib-MenCY-TT-001/-002, Hib-MenCY-TT-003/-004, Hib-MenCY-TT-005/-006, Hib-MenCY-TT-007/-008, Hib-MenCY-TT-009/-010) that evaluated the immunogenicity of doses 1 – 3 of MenHibrix, the According to Protocol (ATP) cohorts for immunogenicity included a total of 1467 U.S. subjects (range per study: 70 to 522 subjects) who received MenHibrix vaccine. All subjects were 5 to 16 weeks of age at first vaccination. Five of these studies (Hib-MenCY-TT-003/-004, Hib-MenCY-TT-005/-006, Hib-MenCY-TT-007/-008, and Hib-MenCY-TT-009/-010) evaluated the immunogenicity of dose 4 of MenHibrix, and across these five studies, the ATP cohorts for immunogenicity included a total of 1458 U.S. subjects (range per study: 42 – 554). All subjects were 11 – 18 months of age at fourth vaccination. Anti-PRP antibodies were measured by Enzyme Linked Immunosorbent Assay (ELISA), while meningococcal responses were measured as titers based on the hSBA assay in the studies provided pivotal immunogenicity data or provided concomitant administration data. The anti-PRP assays and hSBA-MenC and hSBA-MenY assays used in the clinical studies have been reviewed by CBER product reviewers and found to be adequate to support licensure of MenHibrix (see Clinical Serology Assay section).

In the pivotal immunogenicity study (Hib-MenCY-TT-009/-010), the lower bound of the 95% CI for the proportions of subjects with hSBA titers of at least 1:8 following 4 doses of MenHibrix was 96.5% for MenC and 97.0% for MenY; as the lower bound of the 95% CI for the proportions with hSBA titers of at least 1:8 was greater than or equal to 90%, acceptance criteria were met for the immune response to meningococcal serogroups C and Y.

In this study, the proportions of participants with an anti-PRP level ≥0.15 mcg/ml following 3 doses of MenHibrix or PRP-T (U.S. licensed ActHIB) were 100% and 98.2%, respectively. The proportions of participants with anti-PRP level ≥1.0 mcg/ml following 3 doses of MenHibrix or PRP-T were 96.3% and 91.2%, respectively. The anti-PRP GMCs post-dose 3 were 11.0 in MenHibrix participants and 6.5 in PRP-T participants. Pre-fourth dose, 95.9% of MenHibrix and 87.8% of PRP-T subjects had an anti-PRP level ≥0.15 mcg/ml. Pre-fourth dose, the anti-PRP GMTs were 1.6 in MenHibrix subjects and 0.8 in PRP-T recipients. Following the fourth dose, the proportion of MenHibrix subjects with an anti-PRP level ≥1.0 mcg/ml was 99.2%, and anti-PRP GMCs in this group were 34.9. For participants who received a fourth dose of U.S. licensed Hib comparator vaccine PedvaxHIB (PRP-OMP), the proportion of subjects with an anti-PRP level ≥1.0 mcg/ml was 99.2%, and anti-PRP GMCs in this group were 20.2. For the analyses of the percentage of subjects with an anti-PRP level ≥1.0 mcg/ml post-dose 3 and post-dose 4, a non-inferiority criterion (lower limit of the 95% CI ≥-10% for the difference MenHibrix minus control) was pre-specified. In both analyses (post-dose 3 and post-dose 4), the non-inferiority criterion was met.

Reports of Potential Vaccination Failures

There were no reports of serious adverse events interpretable as potential vaccine failures.

Evaluation of Concomitant Vaccination

In participants who received MenHibrix concomitantly with Pediarix (DTaP-IPV-HBV) and Prevnar (PCV7) at 2, 4, and 6 months of age, there was no evidence for reduced antibody response to pertussis antigens (GMC to pertussis toxin, filamentous hemagglutinin, and pertactin), diphtheria toxoid (antibody levels ≥0.1 IU/mL), tetanus toxoid (antibody levels ≥0.1 IU/mL), poliovirus types 1, 2, and 3 (neutralizing antibody levels ≥1:8 to each virus), hepatitis B (anti-hepatitis B surface antigen ≥10 mIU/mL) or PCV7 (antibody levels ≥0.2 mcg/mL and GMC to each serotype) relative to the response in control participants administered PRP-T concomitantly with DTaP-IPV-HBV and PCV7. The immune responses to DTaP-IPV-HBV and PCV7 were evaluated one month following dose 3.

There was no evidence for interference in the immune response to MMR and varicella vaccines (initially seronegative participants with anti-measles ≥200 mIU/mL, anti-mumps ≥51 ED_{50}, anti-rubella ≥10 IU/mL, and anti-varicella ≥1:40) administered at 12 to 15 months of age concomitantly with MenHibrix and PCV7 relative to these vaccines administered concomitantly with PRP-OMP and PCV7. The immune responses to MMR and varicella vaccines were evaluated 6 weeks post-vaccination. Data are insufficient to evaluate potential interference when a 4th PCV7 dose is co-administered with MenHibrix at 12-15 months of age, as the comparator in this study (PRP-T) is not licensed in the U.S. for administration at 12 – 15 months of age.

Lot to Lot Consistency

Lot consistency was evaluated after dose 3 in study Hib-MenCY-TT-009/-010. Criteria for lot consistency were based on ratios of pairwise comparisons of lots (A, B, C) for anti-PRP GMTs and Men C and MenY hSBA GMTs. Equivalence was demonstrated for GMT to PRP and MenC. Equivalence was marginally not met for the GMT to MenY. CBER considered this in the context of the variability of the hSBA for MenY and the CMC information provided on these lots and concluded there were no concerns with respect to lot consistency.

Statistical considerations

The statistical analysis of data related to immune responses to MenHibrix vaccine Hib-MenCY-TT showed that the pre-specified criteria were met. Due to concerns that the immunogenicity analyses related to the lot-to-lot consistency studies were carried out on datasets with over 35 % of the immunogenicity data missing, the statistician investigated the influence of the cut-off on certain immunogenicity results (% of subjects with hSBA-MenC and hSBA-MenY titers greater than or equal to 1:8) by evaluating the data using cutoffs of 1:16 and 1:32. The results showed that there were not significant differences between the evaluations using different cutoff values with respect to the percentage reaching that cutoff. These analyses helped to support using the existing datasets, in spite of the missing data.

Bioresearch Monitoring (BiMo)

An FDA form 483 was issued at site 19848 due to protocol violations, record discrepancies, and inadequacies in investigational drug disposition records. The BiMo reviewer's evaluation led to the conclusion that the inspections did not reveal problems that impact the data submitted in the application (May 13, 2010 memo).

The applicant identified protocol violations of Good Clinical Practice at one of the U.S. study sites, which enrolled subjects in studies Hib-MenCY-TT-009/010, and -011/012. Subjects from this site were excluded from the immunogenicity According To Protocol analyses. Post-hoc sensitivity analyses performed regarding the incidence of fever > 39.5°C, SAEs, new onset chronic diseases (NOCDs), rash, and AEs prompting an ER or physician office visit as well as evaluation of the between group difference for proportions of subjects with anti-PRP concentration $\geq$ 1.0 mcg/mL and proportions of subjects with hSBA-MenC and hSBA-MenY $\geq$ 1:8 post-4th vaccination suggested that elimination of data from this center did not impact the clinical outcomes of study Hib-MenCY-TT-009/-010. Similar sensitivity analyses were not performed for the subjects enrolled at this site in Hib-MenCY-TT-011/-012, as no immunogenicity data were collected in this study, only non-detailed safety data were collected, and the number of subjects affected was smaller (40 total for doses 1 – 3 and 27 total for dose 4) in this study. With this exception, no other concerns regarding data integrity were identified for the clinical studies included in the BLA.

7. Safety

Clinical Studies Safety Data
For a general description of the clinical studies see Section 6.0 of this SBRA.

In five MenHibrix studies included in the BLA (Hib-MenCY-TT-001/-002, Hib-MenCY-TT-003/-004, Hib-MenCY-TT-005/-006, Hib-MenCY-TT-007/-008, Hib-MenCY-TT-009/-010), specific solicited adverse events were monitored for at least four days post-vaccination. Serious and non-serious unsolicited adverse events were monitored during Days 0-30 post-vaccination in these studies. In two Phase 2 and in both Phase 3 studies (Hib-MenCY-TT-005/-006, Hib-MenCY-TT-007/-008, Hib-MenCY-TT-009/-010, and Hib-MenCY-TT-011/-012), specific adverse events of interest (SAEs, new onset chronic disease, rash, AEs resulting in emergency room visits) were followed for 6 months following the last immunization. Across the six studies of doses 1 - 3, there were 26 drop outs due to an adverse event or serious adverse event among 7522 subjects who received MenHibrix. Among subjects administered a fourth dose of MenHibrix, there was one subject who dropped out due to a serious adverse event among 6767 subjects. No specific pattern of clinical importance was noted for the drop-outs. Rates of solicited adverse events reported in study Hib-MenCY-TT-009/-010 differed between participants in the U.S., Mexico, and Australia. The rate differences had no specific pattern which would suggest differences in data collection.

In the six studies of doses 1 - 3, among a total of 7521 subjects who received MenHibrix, there were 11 deaths reported, while there were 7 deaths reported among the 2779 Hib control vaccine (PRP-T or Infanrix hexa [Diphtheria and Tetanus Toxoids and Acellular Pertussis, Hepatitis B, Inactivated Poliovirus Vaccine and *Haemophilus influenzae* type b Vaccine Combined, GSK Biologicals] recipients. Death was reported in an additional subject who had received a non-licensure formulation of Hib-MenCY-TT. In the five studies of dose 4, among the 6687 MenHibrix recipients, there were 2 reported deaths, while there were no deaths reported among the 2267 Hib control vaccine (PRP-T, PRP-OMP, or Infanrix hexa) recipients. Over doses 1 – 3 of the MenHibrix clinical development program, causes of deaths following MenHibrix were due to Sudden Infant Death Syndrome (SIDS) – 6 children; shaken baby syndrome – 1 child; gastroenteritis – 1 child; hypovolvemic shock – 1 child; bronchiolitis/gastroenteritis/dehydration – 1 child; pneumonia – 2 children. In a fourth dose study, a male was diagnosed with febrile seizure approximately 4.5 months after receiving MenHibrix and Prevnar (PCV7). He was discharged from the ER and found unresponsive in his crib the next day. According to the applicant, sudden unexplained arrhythmogenic death was the cause of death on the autopsy report. Another MenHibrix recipient died from multiple injuries sustained in a motor vehicle accident 29 days post-vaccination. All subjects who died had received concomitant immunizations. None of the deaths were assessed by the investigator as being related to vaccination. After reviewing the case narratives, the clinical reviewer concurred. An additional four subjects died in a study which was part of another clinical development program; since children in some treatment arms in that study received MenHibrix at 2, 4, and 6 months of age, blinded SAE data and unblinded deaths were submitted to this BLA. The four deaths were due to Hemolytic Uremic Syndrome and septic shock – 1 child; leukemia – 1 child; SIDS – 2 children. All children had received concomitant vaccinations. In all but one case, the investigator determined the deaths to be unrelated to vaccination. The investigator determined that one case of SIDS was related to vaccination. However, as the SIDS occurred 89 days after vaccination, as well as the fact that other vaccines were administered concomitantly, the clinical reviewer's opinion is that the death cannot be determined to be related to MenHibrix.

Across doses 1 – 3 in studies Hib-MenCY-TT-001/-002, Hib-MenCY-TT-005/-006, Hib-MenCY-TT-007/-008, Hib-MenCY-TT-009/-010, and Hib-MenCY-TT-011/-012, at least one SAE occurring within the 31-day post-vaccination period was reported by 1.8% (137/7444) of subjects in the MenHibrix group and 2.1% (59/2779) of subjects in the PRP-T group. Across studies Hib-MenCY-TT-005, -007, -009, and -011, at least one SAE occurring from Day 0 after dose 1 through the day preceding administration of dose 4 was reported by 4.8% (356/7362) of MenHibrix participants and 5.0% of PRP-T (134/2697) recipients. Across studies Hib-MenCY-TT-005/006, -007/-008, -009/-010, and -011/-012, at least one serious adverse event (SAE) occurring within the 31-day post-vaccination period after dose 4 was reported by 0.5% of subjects in each treatment group (35/6640 MenHibrix participants and 12/2267 Hib control vaccine participants). From day 0 after dose 4 through the end of the extended safety follow-up (ESFU) period, at least one SAE was reported in 2.5% (165/6640) of MenHibrix subjects and in 2.0% (46/2267) of the PRP-T or PRP-OMP participants.

Across studies, MenHibrix was generally no more reactogenic than the Hib control vaccine on the basis of the incidence overall per subject of solicited local and general AEs reported within the 4-day post-vaccination period. Pain was the most frequently reported local AE after doses 1 – 3, occurring in 73.8% of MenHibrix recipients and 73.5% of PRP-T recipients in studies Hib-MenCY-TT-001/-002, -005/-006, -007/-008, and -009/-010. Redness was the most frequently reported local AE after dose 4, reported in 47.8% and 54.9% of MenHibrix and PRP-T or PRP-OMP recipients, respectively, in studies Hib-MenCY-TT-005/-006, -007/-008, and -009/-010. Irritability was the most frequently reported solicited general AE after doses 1 – 3, reported in 88.7% and 90.0% of MenHibrix and PRP-T subjects, respectively in studies Hib-MenCY-TT-001/-002, -005/-006, -007/-008, and -009/-010. Irritability was also the most frequently reported general AE after dose 4, reported in 57.9% and 61.9% of MenHibrix and PRP-T or PRP-OMP participants, respectively, in studies Hib-MenCY-TT-005/-006, -007/-008, and -009/-010. Fever was reported in 42.6% and 43.5% of MenHibrix and PRP-T participants, respectively, across doses 1 – 3 in studies Hib-MenCY-TT-001/-002, -005/-006, -007/-008, and -009/-010 and in 12.7% and 15.4% of MenHibrix and PRP-T or PRP-OMP participants, respectively, following dose 4 in studies Hib-MenCY-TT—005/-006, -007/-008, and -009/-010. There was no evidence of increasing reactogenicity with successive doses in the MenHibrix four dose series.

Post-Marketing Safety Experience

There is no post-marketing safety experience, as MenHibrix is not licensed anywhere at this time.

Pharmacovigilance

A pharmacovigilance plan (PVP) was included in the original submission of the BLA. GSK noted that in the UK Risk Management Plan for their HibMenC vaccine (*Menitorix - Haemophilus influenzae* type b and *Neisseria meningitidis* group C conjugate) that purpura is considered to be a class effect for meningococcal conjugate vaccines. GSK considers purpura to be an important potential risk. GSK will follow up reports of purpura with a targeted questionnaire to obtain a more standardized and detailed description of the cases in order to facilitate detection of any patters or potential risk factors. The questionnaire is presented in Appendix 1, Section 1.16 Risk Management Plans. All spontaneous reports of purpura will be discussed in each US Periodic Safety Update Report (PSUR).

GSK will provide monthly periodic reports, consisting of all US serious, expected adverse event reports, for one year following US licensure of MenHibrix (HibMenCY-TT) vaccine. This will be in addition to expedited reporting of serious unexpected events and filing quarterly periodic safety reports per regulation.

The OBE reviewer did not recommend any changes to the proposed Postmarketing safety surveillance or reporting for MenHibrix.

Post Marketing Requirements (PMRs)

Review of the clinical data in the BLA did not identify a known serious risk related to the use of MenHibrix, a signal of a serious risk related to the use of Menhibrix, or available data that indicated a potential for a serious risk that would trigger any required post-approval safety studies of MenHibrix under section 901 Title IX of the Food and Drug Administration Amendments Act (FDAAA) of 2007.

Post Marketing Commitments (PMCs)

Postmarketing Studies subject to reporting requirements of 21 CFR 601.70.

1. To conduct a Phase III open-label administration (laboratory personnel will be blinded to treatment), parallel-group, controlled, multicenter study to evaluate concomitant administration of *MenHibrix* with rotavirus, 13-valent pneumococcal conjugate and hepatitis A vaccines administered according to a US recommended vaccine schedule.

   The study is entitled "A phase IIIb, open, randomized, controlled, multicenter study to assess the immunogenicity, safety and reactogenicity of Hib-MenCY-TT (GlaxoSmithKline Biologicals' Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine) when administered concomitantly with *Rotarix* (GlaxoSmithKline Biologicals'), *Pediarix* (GlaxoSmithKline Biologicals') and *Prevnar 13* (Pfizer) as compared to *Pentacel* (Sanofi Pasteur) administered concomitantly with *Rotarix* and *Prevnar 13* in healthy infants at 2 and 4 months of age. Subjects will receive a third dose of *Prevnar 13*, *Pediarix* and Hib-MenCY-TT or *Pentacel* at 6 months of age. The study will also assess the immunogenicity, safety and reactogenicity of a fourth dose of Hib-MenCY-TT administered concomitantly with *Havrix* (GlaxoSmithKline Biologicals') compared to *Pentacel* administered concomitantly with *Havrix* at 15 to 18 months of age." The final study protocol will be submitted by December 31, 2012. The study will begin by October 31, 2013. The study will be completed by July 31, 2016. The final study report will be submitted by December 15, 2016.

Postmarketing Studies not subject to reporting requirements of 21 CFR 601.70.

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

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

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

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

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

8. Advisory Committee Meeting

MenHibrix was not presented to the Vaccines and Related Biological Products Advisory Committee (VRBPAC) since review of the data did not raise particular concerns or controversial issues which would have benefited from advisory committee discussion. For children under age 2 years, use of bactericidal antibody as measured by hSBA was discussed at a meeting of the VRBPAC in 2011, and CBER was advised that use of hSBA data would be acceptable to infer effectiveness in this population.

9. Pediatrics

Pediatric Research Equity Act (PREA)

MenHibrix was discussed during the Pediatric Review Committee meeting on August 31, 2011. The committee concurred with Office of Vaccine Research and Review's (OVRR's) recommendation to waive studies of MenHibrix in children 0 to <6 weeks of age and in children 19 months to 17 years of age

10. Other Relevant Regulatory Issues

N/A

11. Labeling

The final draft labels for the carton and associated container were submitted on 4 June 2012, and reviewed and found to be acceptable. The proprietary name MenHibrix was reviewed and found to be acceptable by the Advertising and Promotional Labeling Branch. Although it was noted that there is a potential risk for medication error with Menveo, Menomune, and Menactra, it was concluded that this risk may be minimized by providing packaging that will differentiate MenHibrix from Menveo, Menomune, and Menactra.

The package insert (PI) submitted by the applicant was in the format required by FDA's Final Rule titled "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" published in January 2006. All issues regarding the product labeling and the PI were acceptably resolved after exchange of information and discussions with the sponsor.

12. Recommendations

The BLA review committee recommends approval of the BLA for MenHibrix. As chair of the review committee, I concur.

13. References

1. I. Goldschneider, E.C. Gotschlich, M.S. Artenstein. **Human immunity to the meningococcus I. The role of humoral antibodies.** J Exp Med, 129 (1969), pp. 1307–1326.

2. FDA. Vaccines and Related Biological Products Advisory Committee. Rockville, Maryland. April 6 - 7, 2011.