

Summary Basis for Regulatory Action - Hiberix

Date 5 August 2009
From Jay E. Slater, MD, Chair
Subject Summary Basis for Regulatory Action
BLA# 125347/0
Applicant GlaxoSmithKline Biologicals
Date of Submission 17 March 2009
Proprietary Name Hiberix®
Dosage Forms After reconstitution a 0.5mL solution.
Proposed Indication Booster immunization in children 15 months through 4 years of age, following primary immunization with two (PedvaxHIB) or three (ActHIB) primary doses, for the prevention of invasive disease caused by *Haemophilus influenzae* type b.
Recommended Action Approval
Signatory Authority Action *Office Signatory Authority:
I concur with the summary review
I concur with the summary review and include a separate review or addendum to add further analysis
I do not concur with the summary review and include a separate review or addendum*

Table 1: Review documents used in compiling this SBRA

Review Category	Reviewer--date of review
Clinical Review	Karen Farizo, M.D. – 8 July 2009 and 9 July 2009
Statistical Review	Ghideon Ghebreorgis, Ph.D. – 29 June 2009
Pharmacovigilance Review	David Menschik, M.D. – 27 March and 26 June 2009
CMC Review	Mustafa Akkoyunlu, M.D., Ph.D. – 10 July 2009 Scott Norris – 31 July 2009 Tina Roecklein – 29 July 2009 (Items 1-7 of Form 483)

Review Category	Reviewer--date of review
DPQ/Lot testing	Rajesh Gupta, PhD - 17 July 2009 and 5 August 2009 (Testing Plan)
GST exemption	Rajesh Gupta, PhD – 17 June 2009
Facilities Review	Sean Byrd – 3 August 2009 and 3 August 2009 (Items 8 to 13 of Form 483) Joseph George - 5 August 2009
Biomonitoring	N/A
Advisory Committee Transcript	N/A
Container and Labeling	Maryann Gallagher – 13 May 2009 and 15 July 2009 Karen Farizo, M.D. - 26 June 2009
Proprietary name review	Maryann Gallagher – 19 May 2009

1. Introduction

On 17 March 2009 GlaxoSmithKline Biologicals, Rixensart, Belgium (US License 1617) submitted a Biologics License Application (BLA) for Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate). The proprietary name Hiberix® is proposed for the candidate vaccine. Hiberix® contains no preservative. The lyophilized polysaccharide with lactose is supplied lyophilized in 3 mL monodose vials, for reconstitution with 0.7 mL of saline diluent supplied in pre-filled syringes, prior to intramuscular injection of 0.5mL. Hiberix® is intended for booster immunization in children 15 months through 4 years of age, following primary immunization with two (PedvaxHIB® or Comvax®) or three (ActHIB®) primary doses of a Haemophilus b conjugate vaccine.

2. Background

Hiberix® is a polysaccharide conjugate vaccine that contains as active ingredient capsular polysaccharide (polyribosyl-ribitol-phosphate, PRP) prepared from a strain of Haemophilus. influenzae type b, covalently bound to tetanus toxoid. After purification, the conjugate is lyophilized in the presence of lactose as a stabilizer. The vaccine is reconstituted prior to intramuscular injection, with a liquid saline diluent. Each 0.5 mL dose of Hiberix® contains 10 mcg of purified PRP conjugated to --b(4)-- mcg of tetanus toxoid, and 12.6 mg of lactose.

Hiberix® was licensed in Germany in 1996 and is now registered in 98 countries as a stand-alone vaccine and in more than 100 countries when combined with other vaccines. Generally, in these countries Hiberix® is used as a primary series of three doses administered in the first 6 months of life and a booster dose in the second year of life. From launch in 1996 through 30 November 2008, approximately -b(4)- million doses of Hiberix® were distributed worldwide.

Currently, there are two other manufacturers of licensed Haemophilus b Conjugate Vaccines in the U.S. Merck & Co., Inc. produces PedvaxHIB® [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)] and COMVAX® [Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine]. Sanofi Pasteur 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]. All of these vaccines are approved in the U.S. for primary and booster immunization against invasive disease due to H. influenzae type b, with the exception of TriHIBit®, which is approved for booster immunization only.

In the U.S., a nationwide shortage of Haemophilus b Conjugate Vaccine began in December 2007 [due to a voluntary recall of certain lots of PedvaxHIB® and COMVAX® and suspended production of these two vaccines.](#)⁽¹⁾ The shortage resulted in a recommendation by the Centers for Disease Control and Prevention (CDC) to defer the Haemophilus b Conjugate Vaccine booster (routinely administered in the second year of life) for children who are not at high risk of infection with H. influenzae type b, temporarily, until restoration of the vaccine supply. The recommendation for deferral of booster vaccination was in effect from 18 December 2007 through 25 June 2009.^{1, [2]} On 26 June 2009, coinciding with an increase in the number of doses of ActHIB® and Pentacel® available in the U.S., the CDC recommended reinstatement of the booster dose for children 12-15 months of age who have completed a primary series with Haemophilus b Conjugate Vaccine.² In their 26 June 2009 recommendation, the CDC indicated that older children for whom the booster dose was deferred should receive their booster dose at the next routinely scheduled visit or medical encounter.² As of 26 June 2009, although supply is sufficient to reinstate the booster dose and begin catch-up vaccination, supply is not yet ample enough to support a mass notification process to contact all children with deferred booster doses.²

Application of Accelerated Approval Regulations

Although not studied under U.S. IND, Hiberix® has been evaluated in clinical studies that supported its first licensure in Germany in 1996 and subsequent licensure in other countries. Prior to submission of this BLA, CBER reviewed the available data which would support licensure and determined that the available data on the effectiveness of Hiberix® for primary and/or booster immunization were not sufficient to support traditional approval. Limitations of the studies included lack of racial/ethnic diversity of study populations, lack of concomitant administration data with certain other vaccines that are used on the same schedule in the U.S., limited data comparing Hiberix® to a U.S. licensed vaccine, limited data on priming using the schedule intended for approval in the U.S., and limited data on booster vaccination in subjects previously primed with a U.S. licensed vaccine on a U.S. schedule. In view of the shortage of Haemophilus b Conjugate Vaccine, and with concurrence from its Office of General Counsel, CBER agreed to consider a BLA for Hiberix® for booster immunization under the accelerated approval regulations, 21 CFR Part 601, Subpart E.

Accelerated approval may be granted for certain biological products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments. CBER stipulated that accelerated approval of Hiberix® for booster immunization could only be granted in the context of a shortage in the supply of the existing, licensed Haemophilus b Conjugate Vaccines. CBER also stipulated that accelerated approval of Hiberix® for booster immunization would be subject to the requirement that GSK conduct

an adequate and well-controlled safety and immunogenicity study to verify the clinical benefit of booster immunization with Hiberix®.

GlaxoSmithKline Biologicals has submitted this BLA in response to the existing shortage of Haemophilus b conjugate vaccines in the U.S. Because of this shortage, CDC (as of 19 December 2007) has recommended that health care providers refrain from administering the 12-15 months booster dose except to children in specific high risk groups (American Indian and Alaska Natives; and children with asplenia, sickle cell disease, human immunodeficiency virus infection and certain other immunodeficiency syndromes, and malignant neoplasms) and their close contacts. GlaxoSmithKline Biologicals requested and was granted priority review, and accelerated approval for this BLA under 21 CFR 601 subpart E – Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses.

3. Chemistry Manufacturing and Controls (CMC)

General Manufacturing Summary

Hiberix® consists of capsular polysaccharide from Haemophilus influenzae type b covalently bound to tetanus toxoid, and lyophilized in the presence of lactose for stability. The Hib polysaccharide (PRP) is manufactured by GSK in -b(4)-, Belgium[3]. The tetanus toxoid is manufactured by --b(4)- - in ----b(4)- ----and is subsequently -----b(4)----- by GSK at Rixensart, Belgium. The -----b(4)- ----- drug substance, formulation of the drug product, and Quality Control tests are performed at Rixensart. Filling and lyophilization of the drug product are also performed by GSK at the -b(4)- site.

1 Page determined to be not releasable: b(4)

Drug Product

The Hiberix® vaccine contains the following components:

Table 2: Composition of Hiberix Vaccine

Ingredients	Quantity (per dose 0.5 mL)
<i>Haemophilus influenzae</i> type b capsular Polysaccharide (Hib) conjugated to tetanus toxoid (TT)	10 µg Hib and ~ 25 µg of TT
Lactose	12.6 mg
Sodium Chloride	-b(4)-
Water for Injection	q.s. ad 0.5 ml

- Pharmaceutical form: lyophilized product to be reconstituted with saline diluent prior to injection
- Presentation: lyophilized monodose in 3 mL type-b(4)- glass vials for reconstitution with 0.7 mL saline.
- Storage: +2°C to +8°C
- Overfill: a formulation overage of approximately -b(4)- is applied in order to guarantee an injectable dose of 0.5 mL containing 10 µg of Hib PS

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

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

There is no intermediate produced between the final bulk stored at -b(4)- and the end of lyophilization. Monitoring and controls during Hiberix formulation consist of integrity testing of filters used for -b(4)- sterilization and -b(4)- measurement. During aseptic filling operations in the ---b(4)- --- system, control of fill volume is performed. -b(4)- of the final container--b(4)- system and ---b(4)- ---- of the final container after reconstitution with ----b(4)- ----- are monitored for Hiberix® vaccine vials.

Validation of the Hiberix® drug product production process is performed through the demonstration of process consistency. A retrospective validation in which consistency of the Hiberix® process was assessed through the analysis of data of -b(4)- lots manufactured at -b(4)- (formulation) and -b(4)- (filling/lyophilization) was included in the BLA. These -b(4)- retrospective validation lots were compared to -b(4)- lots formulated, filled, and lyophilized at -b(4)- Batch analysis data was provided for all lots. All lots complied with the release specifications. In addition, aseptic operations are validated according to regulatory guidelines. This includes media formulation studies and media fill studies.

The -----b(4)- ----- the active substance is lactose. Lactose included in the formulation of Hiberix® is tested according to the current -----b(4)-----
----- Lactose used in Hiberix® is manufactured from milk sources in the USA.

Control of Drug Product:

Specifications for release of Hiberix® 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 with GSK.

Table 3: Specifications for Hiberix® Final Container Vaccine

Test	Specifications
Description	-----b(4)-----
Identity Haemophilus influenza type B antigen by -b(4)-	---b(4)---
Sterility test -----b(4)----- --	----b(4)---
Sterility test -----b(4)----- --	---b(4)----

-----b(4)-----	-----b(4)-----
Water content by ----b(4)----	-----b(4)-----
Endotoxin content -----b(4)-----	-----b(4)-----
-----b(4)-----	-----b(4)-----
-----b(4)-----	-----b(4)-----
-b(4)-	-----b(4)-----

Batch analysis results are presented in the BLA file. Batches -----b(4)- ----- are fully representative of the manufacturing process for US commercial product. Additional batches 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.

A list of current reference standards used in the testing of the Hiberix® final container is contained in the BLA file. The control of reference standards and materials for drug product is similar to the drug substance.

Date of Manufacture:

GSK proposes the start date of filling into final containers as the Date of Manufacture. CBER concurs with this proposal.

Stability:

Hiberix® 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 that support 36 months of storage at 2-8°C. Hiberix® final container vaccine lots were also included in accelerated stability studies at -----b(4)-----. All lots met the specifications.

Stability data were obtained on Hiberix® final container vaccine reconstituted with saline diluent. Stability was assessed after reconstitution with saline diluent and storage ---b(4)- ---- for 24 hours at

---b(4)-----. Specifications were met for all parameters tested. GSK will perform additional studies on stability of reconstituted vials.

GSK will perform on-going -b(4)- stability studies on -----b(4)- ----- bulk conjugate per year.

The 0.9% sodium chloride diluent is manufactured -----b(4)-----

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Refer to Ms. Tina Roecklein's review memorandum, 4 August 2009, for detailed information on stability studies.

Lot Release

For routine lot release, the firm will submit samples and a Lot Release Protocol for each final container lot to CBER. During review of the BLA, CBER agreed that the initial lots for Hiberix, consisting of-b(4)-batches and approximately b(4)-million doses, would be released using a Lot Release Protocol submitted on 31 July 2009.

The firm agreed to include additional testing in future Lot Release Protocols, according to a schedule agreed to in the BLA.

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

The firm submitted three launch lots in support of approval, AHIBC243A, AHIBC251A, and

AHIBC262A. The three lots were tested at CBER for:

- sterility;
- endotoxin (LAL);
- residual moisture (methanol extraction Karl Fischer Coulometric Method);
- identity test by ELISA;
- molecular distribution coefficient;
- free carrier protein;
- free polysaccharide (ELISA); and
- polysaccharide (High Performance Anion Exchange – Pulsed Amperometric Detection)

The firm also submitted three bulk lots: -----b(4)-----.

These were tested by CBER for:

- molecular distribution coefficient;
- free carrier protein;
- residual cyanide;
- free polysaccharide (ELISA);
- protein (Lowry); and
- polysaccharide (Orcinol).

All bulk and final container lots tested were within specifications.

General Safety Testing (GST)

The GST was performed for each lot of Hiberix® final container vaccine in the past as part of the release specifications until 2002, when this test was eliminated by GSK in agreement with --b(4)-----, and other international regulatory authorities. GSK submitted a request for exemption from the US GST in accordance with 21 CFR 610.11 in the BLA. GSK provided information on the manufacturing process and quality control tests performed on Hiberix® to adequately characterize the product and validate its safety, as follows:

1. Prior to discontinuing the test, all -b(4)- lots complied with the GST requirements.
2. The implementation of various technological advances in the manufacture and aseptic processing of products as well as incorporation of stringent in-process and final product quality control requirements obviate the need to perform the GST.
3. Release testing for Hiberix, which includes sterility, endotoxin content, and identity, provides assurance of safety, purity, and potency of the product.

Based on past testing history and the additional information provided, CBER concurred with GSK's request for exemption from the GST.

Clinical Serology Assays

Three separate methods were used to measure anti-PRP antibodies in the seven clinical trials submitted in this BLA. These assays are -----b(4)-----, GSK -b(4)-, and ----b(4)- ----- assay was used in studies DTPa-HBV-020, DTPa-IPV-13p, DTPa-IPV-026, DTPa-HPV-IPV-010, DTPa-HBV-IPV-012. GSK -b(4)- was used in study DTPa-HBV-032. -b(4)---- -b(4)- was used in clinical study DTPa-HBV-IPV-035. In all three methods an anti-PRP antibody concentration ≥ 0.150 $\mu\text{g/ml}$ is considered as seropositive, while ≥ 1 $\mu\text{g/ml}$ of antibody concentration as seroprotective. Seropositivity suggests that serum contains sufficient antibodies to prevent systemic (invasive) Hib infection. Seroprotectivity suggests that the seropositive

levels of protective antibodies would last at least one year. These definitions are internationally accepted and are derived from scientific literature reporting experiences with conjugate PRP vaccines.

The validation reports for the -b(4)- GSK -b(4)- and ----b(4)- ---- demonstrate that these methods accurately measure antibodies against PRP in human sera.

Facilities Review

Pre-approval inspection of GSK's facilities in Belgium was conducted on 3 June to 12 June 2009. Thirteen observations were presented to the firm on Form FDA 483 on 12 June 2009. These observations were addressed to the reviewers' satisfaction in a submission to the file on 6 July 2009.

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

In a submission received on 8 May 2009, GSK described their strategy to supply-b(4)-million doses of Hiberix® to the US market by the end of 2009. This strategy includes what is described as "minor packaging and labeling changes...to package Hiberix® in ---b(4)----- following approval of this facility. These changes are planned to be provided to the BLA and review team appropriately or filed as an annual reportable change if the Hiberix® BLA is approved prior to [7 August 2009]." GSK has not, as of the date of this memorandum, transitioned to the --b(4)--- facility for Hiberix® packaging and labeling use. Therefore, this information will be included in GSK's next Annual Report after approval of the facility (STN ----b(4)-----) and the Hiberix® BLA. Review and Inspection related to the Marietta, PA file (STN ---b(4)-----) has been completed. The inspection of this facility revealed no objectionable conditions and a 483 was not issued. The packaging and labeling to be used in the ---b(4)----- were provided in a submission on 4 August 2009, and were found to be acceptable.

Environmental Assessment

Regarding environmental assessments, it was noted that GSK stated that this submission meets 21 CFR 25.31(c), i.e., a categorical exclusion from environmental assessment requirements. The DMPQ reviewer agreed that this product is categorically excluded from an environmental assessment.

4. Non-clinical/Toxicology

During the pre-BLA meeting for Hiberix® (2 February 2009; minutes 27 February 2009) CBER concurred that - given the extent of human experience with Hiberix® - non-clinical data were not needed in the BLA.

5. Clinical Pharmacology

During the pre-BLA meeting for Hiberix® (2 February 2009; minutes 27 February 2009) CBER concurred that - given the extent of human experience with Hiberix® - non-clinical data were not needed in the BLA.

6. Clinical/ Statistical-Efficacy

(from Dr. Farizo's Clinical Review – Executive Summary)

General Description of Clinical Studies

This BLA for licensure of Hiberix® for booster immunization under the accelerated approval regulations contains reports of seven clinical studies in which Hiberix® was used for booster immunization and two supportive primary immunization studies (see Table 5 and 6). None of the Hiberix® booster immunization studies included a

comparator group that received a booster dose with a U.S. licensed Haemophilus b Conjugate Vaccine. These seven clinical studies provide safety data on a total of 1,008 children who received Hiberix® as a booster dose and 1,396 infants who received Hiberix® for primary immunization. The clinical studies were conducted in Europe, Latin America, and Canada. For studies in which information on race/ethnicity was provided, nearly all subjects were Caucasian. Approximately half of subjects were male. Across the seven booster immunization studies, the mean age at receipt of Hiberix® ranged from 15.9 to 18.7 months. Of the 1,008 subjects who received Hiberix® as a booster dose, 172 (17.1%) were 11 to 14 months of age, 642 (63.7%) were 15 to 18 months of age, and 194 (19.2%) were 19 to 25 months of age at the time of vaccination. In the booster immunization studies, Hiberix® was administered concomitantly with one of the following vaccines manufactured by GSK: Infanrix® [Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, DTaP]; DTaP combined with Hepatitis B Vaccine (DTaP-HBV, not licensed in the U.S.); Pediarix® [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine Combined, DTaP-HBV-IPV]; or Kinrix® (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine, DTaP-IPV). The formulations of Infanrix, Pediarix®, and Kinrix® used in the booster studies of Hiberix® were the same as the U.S. licensed vaccines except that in most instances, they also contained 2-phenoxyethanol as preservative. In the booster immunization studies, Pediarix® and Kinrix® were used in schedules not approved in the U.S. Among 1,008 subjects in the booster immunization studies who were evaluated for safety, 530 had been primed with Hiberix®, 235 with ActHIB®, 217 with HibTITER® (PRP-diphtheria CRM₁₉₇ protein conjugate; no longer licensed in the U.S.) and 26 with PedvaxHIB®.

Table 4: Hiberix®Booster Immunization Studies

Study [No.] Country	Study Start/End	Priming History	Relevant Booster Study Groups	Number of subjects- Total Vaccinated Cohort	Number of subjects- Per Protocol Immuno- genicity Cohort
DTPa-HBV-032 [208140/032] Argentina Brazil	June 1997/ May 1999	2, 4, 6 months: DTPa-HBV + Hiberix	DTPa-HBV + Hiberix	146	84
DTPa-IPV-013p [213503/013] Canada	Nov 1995/ March 1996	2, 4, 6 months: Kinrix + Hiberix	Kinrix + <i>Hiberix</i>	64	64
DTPa-HBV-020 [208140/020]	June 1995/ Feb 1996	3, 4, 5 months: DTPa-HBV + Hiberix	DTPa-HBV + Hiberix	138	138

Germany					
DTPa-IPV-026 [213503/026] Lithuania	Mar 1997/ July 1997	3, 4.5, 6 months: Pediarix + Hiberix or Pediarix + ActHIB (~2/3 Hiberix primed)	Infanrix + Hiberix + OPV Vaccine	92	60
DTPa-HBV-IPV-010 [217744/010] Canada	Sep 1995/ Nov 1995	2, 4, 6 months: Pediarix + ActHIB	Pediarix + Hiberix	43	42
DTPa-HBV-IPV-035 [21744/035] Germany	Dec 1997/ Dec 1998	3, 4, 5 months: Pediarix + Hiberix or Pediarix + ActHIB or Pediarix + HibTITER or Pediarix + PedvaxHIB or Infanrix + ORIMUNE + ActHIB	Pediarix + Hiberix	150	56
DTPa-HBV-IPV-028 [21744/028] Germany	Apr 1997/ Nov 1998	3, 4, 5 months: Pediarix + Hiberix or Pediarix + ActHIB or Pediarix + HibTITER or Pediarix + PedvaxHIB or Infanrix + ORIMUNE + ActHIB	Pediarix + Hiberix	375	NA
			Total Hiberix	1008	414

The symbol “+” is used to indicate that two vaccines are administered concomitantly in two separate injections.

DTPa-HBV = diphtheria-tetanus acellular pertussis hepatitis B virus vaccine, same antigens as in Pediarix

Kinrix = Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine, GSK (licensed in U.S. for use in children 4-6 years of age following 4 previous doses of DTaP using Infanrix and/or Pediarix for the first 3 doses and Infanrix for the fourth dose).

Infanrix = Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (licensed in U.S. for 5 dose DTaP series in children 6 weeks to 7 years of age)

Pediarix = Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine Combined (licensed in U.S. as a 3-dose primary series in children 6 weeks to 7 years of age)

ActHIB = Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)

ORIMUNE = oral poliovirus vaccine (no longer licensed in U.S.)

HibTITER = Haemophilus b Conjugate Vaccine (Diphtheria CRM197 Protein Conjugate) (no longer licensed in U.S.)

PedvaxHIB = Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)

Source: m 2.5 clinical-overview.pdf, pages 17-19

Table 5: Hiberix®Supportive, primary Immunization Studies

Study [No.] Country	Study Start/ Study End	Study Groups	Number of subjects- Safety cohort (all vaccinated subjects)	Number of subjects- Per Protocol Immuno- genicity Cohort
DTPa-HBV- IPV-011 [21744/011] Germany	Nov 1995/ Dec 1997	Hiberix + Pediarix ActHIB + Pediarix HibTITER + Pediarix PedvaxHIB + Pediarix Infanrix + ActHIB + ORIMUNE	1177 1174 1174 1171 776	NA
DTPa-HBV- IPV- 012 [21744/012] Lithuania	Nov 1995/ July 1996	Hiberix + DTPa-HBV- IPV ActHIB + DTPa-HBV- IPV HibTITER + DTPa- HBV-IPV PedvaxHIB + DTPa- HBV-IPV	219 110 110 110	202 102 100 105
		TOTAL Hiberix	1396	202

Pediarix = Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine Combined (licensed in U.S. as a 3-dose primary series in children 6 weeks to 7 years of age)

ActHIB = Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)

HibTITER = Haemophilus b Conjugate Vaccine (Diphtheria CRM197 Protein Conjugate) (no longer licensed in the U.S.)

PedvaxHIB = Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)

Infanrix = Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (licensed in U.S. for 5 dose DTaP series in children 6 weeks to 7 years of age)

ORIMUNE = oral poliovirus vaccine (no longer licensed in the U.S.)

Source: m 2.5 clinical-overview.pdf, page 20

Clinical Studies Effectiveness Data

The evaluation of effectiveness of Hiberix® for booster immunization was based on immunogenicity data, 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[4] and data from passive antibody studies,[5] an anti-PRP level of 0.15 mcg/ml has been accepted as a minimum

protective level, correlating with at least short term protection, and a level of 1.0 mcg/ml as a long-term (one-year) protective level.[6],[7]

Across six booster immunization studies that evaluated the immunogenicity of Hiberix®, the According to Protocol (ATP) cohorts for immunogenicity included a total of 415 subjects (range per study: 42 to 108 subjects) who received Hiberix®. Of these subjects, 30 subjects were 11 to 14 months of age, 316 subjects were 15 to 18 months of age, and 69 subjects were 19 to 25 months of age. Approximately 75% (N=306) of subjects had been primed with Hiberix®; 89 subjects from three different studies had been primed with ActHIB; 11 subjects had been primed with HibTITER; and 9 subjects had been primed with PedvaxHIB. Anti-PRP antibodies were measured by either a ---b(4)- ----- b(4)-----) or an -----b(4)-----, depending on the study. The anti-PRP assays used in the clinical studies have been reviewed by CBER and are considered acceptable for the evaluation of the effectiveness of Hiberix® for booster immunization. Across the six studies, the proportion of subjects with a pre-booster vaccination anti-PRP level >0.15 mcg/ml ranged from 71.4% to 97.6%. All subjects had an anti-PRP level >0.15 mcg/ml following a booster dose of Hiberix®. The proportion of subjects with a pre-booster vaccination anti-PRP level >1.0 mcg/ml ranged from 12.7% to 65.9%. All but three subjects had an anti-PRP level >1.0 mcg/ml following a booster dose of Hiberix®. Across the six studies, pre-booster vaccination anti-PRP GMCs ranged from 0.25 mcg/ml to 1.9 mcg/ml. Following a booster dose with Hiberix®, anti-PRP GMCs ranged from 47.8 mcg/ml to 137 mcg/ml, corresponding to a pre- to post-booster increase in anti-PRP GMCs ranging from 45-fold to 188-fold. In one of the supportive primary immunization studies, one month after three priming doses with Hiberix®, all 202 subjects had an anti-PRP level >0.15 mcg/ml and 96% had an anti-PRP level >1.0 mcg/ml; the post-vaccination anti-PRP GMC was 7.2 mcg/ml. In summary, the available immunogenicity data, obtained in generally healthy children who were almost exclusively Caucasian and predominantly 15 to 18 months of age, demonstrate a robust immune response against PRP elicited by a booster dose of Hiberix® administered concomitantly with various DTaP combination vaccines that contained components of Pediarix®. Although most subjects had been primed with Hiberix®, the robust immune response after booster vaccination appeared to be consistent, regardless of the Haemophilus b Conjugate Vaccine used for priming. Data are not available on the effectiveness of Hiberix® in children who may be at increased risk for invasive disease due to H. influenzae type b, including American Indian/Alaska Native children and children with certain immunosuppressive conditions.

Reports of Potential Vaccination Failures

In a search of their worldwide safety database through 30 November 2008 for reports describing potential vaccination failures, GSK identified 20 cases in which the patients had completed the primary vaccination schedule (at least 3 doses) and invasive H. influenzae type b infection had been confirmed by laboratory testing.

In 8 (40%) of the 20 cases, the patients were reported to have received at least one priming dose with a DTP-based combination vaccine mixed with Hiberix® in the same syringe just prior to administration. Five (63%) of these 8 patients had been administered DTP whole-cell pertussis-based vaccines as part of the primary series. In 11 (55%) of the 20 reports, the patients were more than 18 months of age when they experienced invasive H. influenzae type b disease. In 10 (91%) of the 11 reports, the

patients had not received a booster dose of Haemophilus b Conjugate Vaccine following the 3 dose primary series. The reporting frequency of lack of efficacy was approximately 0.4 reports per million doses distributed based on ---b(4)- ---- doses of Hiberix® having been distributed through 30 November 2008.

Statistical considerations

The statistical review covered the concept protocol for the confirmatory study planned to be conducted in the US (study HIB-097) and the seven studies proposed by GSK as core-studies to support licensure. Since the latter studies occurred outside the US, and not under IND, statistical input by CBER was not required. Relevant statistical issues related to confirmatory study HIB-097 were addressed.

Bioresearch Monitoring

Bioresearch monitoring inspections for studies included in the Hiberix® BLA were waived. This recommendation was based, in part, on the expectation that such inspections may not yield useful information for studies that were conducted in the mid- to late-1990s.

For one of the booster immunization studies, Study DTPa-IPV-026 (Section 7.1.4), GSK suspected fraud in data collection at one of the study sites. The site was closed and subjects from the site were excluded from the According to Protocol analyses. 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

(from Dr. Farizo's Clinical Review - Executive Summary)

For a general description of the clinical studies see Section 6.0 of this SBRA.

In the Hiberix® studies included in the BLA, specific solicited adverse events were monitored during Days 0-4 post-vaccination. Serious and non-serious unsolicited adverse events were monitored during Days 0-30 post-vaccination. Across the seven booster immunization studies, there were no drop outs due to an adverse event among 1,008 subjects who received Hiberix®.

In the seven booster immunization studies, no deaths were reported following receipt of Hiberix®. Among 1,396 infants who received Hiberix® and Pediarix in a supportive primary immunization study, there were two deaths. One infant died of Sudden Infant Death Syndrome (SIDS) 18 days post-vaccination. One infant died 36 days post-vaccination, presumably due to a convulsive disorder of undetermined etiology that had initially manifested four days post-vaccination. Among 4,625 infants who received another Haemophilus b Conjugate Vaccine in the primary immunization studies, there were two deaths, including one case of SIDS. Another infant with an unspecified immune deficiency identified at autopsy, died of respiratory arrest following seizures, hypoxic cerebral damage, and sepsis.

Across the seven booster immunization studies, two subjects reported a serious adverse event occurring within 31 days following receipt of Hiberix®. One subject had impaired consciousness due to accidental drug ingestion. One subject developed pneumonia 12 days post-vaccination. In the largest of the two supportive primary immunization studies, subjects received three doses of Pediarix administered concomitantly with either Hiberix® (N=1177), ActHIB® (N=1173), HibTITER® (N=1174), or PedvaxHIB® (two doses) (N=1171); a fifth group received Infanrix®, oral poliovirus

vaccine (OPV; no longer licensed in the U.S.), and ActHIB® (N=776). The percentage of subjects reporting a serious adverse event within 31 days after any dose was 1.9% following Pediarix® + Hiberix®, 1.5% following Pediarix® + ActHIB®, 1.2% following Pediarix® + HibTITER®, 1.4% following Pediarix® + PedvaxHIB®, and 1.8% following Infanrix® + ActHIB® + OPV. The nature and timing of the serious adverse events raised no particular safety concerns about Hiberix®.

In the largest of the booster immunization studies, solicited injection site reactions (pain, redness, and swelling) occurred commonly (15% to 25% of subjects) following Hiberix®. Pain that prevented usual activities, redness >20 mm in diameter, and swelling >20 mm in diameter each occurred in approximately 1% to 2% of subjects. The occurrence of fever was actively monitored with daily temperature measurements during the period Days 0-3 after booster vaccination with Hiberix® administered concomitantly with Pediarix®. Approximately 35% of subjects reported post-vaccination fever >38oC and approximately 4% reported fever >39.5oC. Based on the data from this study, it is not possible to draw conclusions about attribution of post-vaccination fever to Hiberix® and/or Pediarix®, as all subjects received these vaccines concomitantly.

Post-Marketing Safety Experience

The BLA includes a review of the post-marketing safety experience with Hiberix® during a 12 year period when approximately b(4) million doses of Hiberix® were distributed in other countries. The ten most frequent, spontaneously reported adverse events for Hiberix® were pyrexia, various local injection site reactions, and drug administration error. There were 27 reports with a fatal outcome (approximately 5 per b(4) million doses distributed). The disease processes in these cases were consistent with the prevalent causes of death in infants and children in the first two years of life and no unusual patterns were noted. In response to three post-marketing reports, GSK has been closely monitoring leukocytoclastic vasculitis. In addition to medical evaluation and expedited reporting of individual case reports, GSK will follow-up reports of leukocytoclastic vasculitis with a targeted questionnaire to obtain a standardized, detailed description of the cases. In response to one post-marketing report in an adult who received Hiberix®, GSK plans to follow-up reports of type III, immune complex-mediated reactions on an individual basis.

Table 6. Overview of the 10 most frequently reported events for Hiberix®, spontaneous post-marketing reports, all age groups (3 June 1996 through 30 November 2008)

System Organ Class	Preferred Term	Number of Events	Reported frequency per 100,000 doses distributed
General disorders and administration site conditions	Pyrexia	235	0.43
General disorders and administration site conditions	Injection site erythema	182	0.33
General disorders and administration site conditions	Injection site oedema	104	0.19
Psychiatric disorders	Crying	95	0.17

General disorders and administration site conditions	Injection site swelling	82	0.15
Injury, poisoning and procedural complications	Drug administration error	80	0.15
General disorders and administration site conditions	Injection site reaction	79	0.14
Skin and subcutaneous tissue disorders	Erythema	79	0.14
General disorders and administration site conditions	Injection site pain	66	0.12
General disorders and administration site conditions	Local reaction	55	0.10

Pharmacovigilance

A pharmacovigilance plan (PVP) was included in the original submission of the BLA. The submitted PVP was generally adequate although the sponsor was asked, in a letter dated 30 April 2009 and a teleconference on 26 May 2009, to provide additional details of enhanced pharmacovigilance procedures for evaluating specified adverse events. The sponsor adequately addressed CBER's comments in a submission to the BLA, 18 June 2009.

Post Marketing Requirement and Commitments

Clinical Trial Post Marketing Requirement

As required by the accelerated approval regulations, GSK has committed to conduct a clinical trial in the U.S. to evaluate the safety and immunogenicity of primary and booster vaccination with Hiberix, relative to a U.S. licensed Haemophilus b Conjugate Vaccine. The trial will be conducted in a study population that is representative of the racial/ethnic composition of U.S. children. In the trial, Hiberix® will be administered concomitantly with other vaccines that are recommended for U.S. children. The planned trial is intended to provide confirmatory evidence of the clinical benefit of booster immunization with Hiberix®, in accordance with the accelerated approval regulations. The planned trial is also intended to fulfill the PREA requirement for pediatric studies for the age group 6 weeks to 14 months of age and to support approval of Hiberix® for a 3-dose primary series. GSK expects to initiate the study by September 2009 and to submit the final study report by January 2013.

Based on a detailed review of clinical studies safety data and postmarketing safety data on Hiberix® that were submitted to the BLA, CBER does not require any postmarketing studies under the Food and Drug Administration Amendments Act (FDAAA) of 2007, Section 901, Title IX. Although the postmarketing study described above is required under PREA and the accelerated approval regulations (21 CFR Part 601, Subpart E), this study is not required under FDAAA for any of the following purposes:

- To assess a known serious risk related to the use of Hiberix®
- To assess signals of serious risk related to the use of Hiberix®
- To identify an unexpected serious risk when available data indicate the potential for a serious risk.

The available safety data on Hiberix® raised no particular concerns about the safety of booster vaccination with Hiberix®. While much of the booster immunization data were obtained in children previously primed with Hiberix®, there is no compelling reason to

think that the overall safety profile of Hiberix® would differ substantially depending on the particular Haemophilus b Conjugate Vaccine used for priming. In view of the shortage of Haemophilus b Conjugate Vaccines which resulted in deferral of routine booster vaccination from 18 December 2007 through 25 June 2009, and insufficient supplies to currently support mass catch-up vaccination, the clinical studies immunogenicity and safety data, combined with the post-marketing experience with Hiberix® in other countries, support accelerated approval of Hiberix® for booster immunization for the prevention of invasive disease due to H. influenzae type b. The available clinical data are considered adequate to support use of Hiberix® for booster immunization in children 15 months through 4 years of age. The number of children 12 to 14 months of age who were evaluated in clinical studies of booster immunization with Hiberix® was not sufficient to support approval for this age group.

Post Marketing Commitments (PMCs)

CBER concurred with GSK's written non-clinical commitments as described in their 31 July 2009 submission to the BLA.

8. Advisory Committee Meeting

It was determined that review of the vaccine by the Vaccines and Related Biological Products Advisory Committee was not required.

9. Pediatrics

Pediatric Research Equity Act (PREA)

Based on clinical studies of booster immunization with Hiberix® in children 15 to 18 months of age, GSK has requested approval of Hiberix® for booster immunization in children 15 months to 4 years of age (prior to 5th birthday). It is anticipated that the safety profile of Hiberix®, when used for catch-up booster vaccination in children 19 months through 4 years of age, would not meaningfully differ from that observed in clinical studies of children 15 to 18 months of age. Extrapolation of immunogenicity data on booster vaccination with Hiberix® from children 15 to 18 months of age to older children 19 months through 4 years of age is supported by previous experience demonstrating robust anti-PRP immune responses following unconjugated Haemophilus b Polysaccharide Vaccine in children 4-5 years of age.[\[8\]](#)

A waiver to conduct studies of Hiberix in children 0 to <6 weeks of age and in children 5 to 17 years of age is justified because in these age groups, use of Hiberix® is not thought to represent a meaningful therapeutic benefit over existing vaccination schedules and Hiberix® is not likely to be used in a substantial number of patients. In addition, for children 5 to 17 years of age, necessary studies with Hiberix® would be impossible or highly impracticable.

Deferral of a study of Hiberix® in children 6 weeks to 14 months of age is justified since waiting for results of such a study would unnecessarily delay approval of Hiberix® for booster immunization. Availability of Hiberix® for booster immunization is expected to help in restoring and maintaining an adequate vaccine supply and in accomplishing catch-up vaccination for children whose booster dose has been deferred because of the shortage of Haemophilus b Conjugate Vaccines. GSK has committed to conduct a study to evaluate the safety and immunogenicity of Hiberix® for primary immunization in infants beginning as early as 6 weeks of age, with follow-up through 6 months after the booster dose administered at 15 to 18 months of age. This study is expected to be initiated by September 2009 and the final report submitted by January 2013.

CBER concurs with GSK's proposals. CBER's justifications for granting a partial waiver and deferral of studies in the specified age groups are presented in Sections 10.3.1, 10.3.2, and 10.3.3 of the clinical review. The proposed approach to meeting the requirements of PREA for Hiberix® were discussed with FDA's Pediatric Review Committee on 24 June 2009. The Committee concurred with the approach.

10. Other Relevant Regulatory Issues

N/A

11. Labeling

The labels for the carton and associated container were reviewed and found to be acceptable. The proprietary name Hiberix® was approved by the Advertising and Promotional Labeling Branch, with concerns. There is a potential risk for medication errors with Havrix®. However, these risks may be minimized by providing packaging that will differentiate Hiberix® from Havrix®.

The package insert 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. No major labeling issues were identified. Specific comments on the labeling proposed by GSK were itemized in a separate review memo dated 26 June 2009.

All issues were acceptably resolved after exchange of information and discussions with the sponsor.

12. Recommendations

The committee recommends approval of the BLA.

[1]. CDC. Interim recommendations for the use of Haemophilus influenzae type b (Hib) conjugate vaccines related to the recall of certain lots of Hib-containing vaccines (PedvaxHIB and Comvax). MMWR 2007;56:1318-20.

[2]. CDC. Updated recommendations for use of Haemophilus influenzae type b (Hib) vaccine: reinstatement of the booster dose at ages 12-15 months. MMWR 2009;58:673-674.

[3] The manufacture of capsular polysaccharide was originally licensed at the GSK site at Rixensart. In order to allow for an increase in capsular polysaccharide manufacturing capacity, an -----b(4)-----. The ----b(4)----(-b(4)-) is located at the GSK site at -b(4)-. All US product will be manufactured at -b(4)-.

[4]. Peltola H, Kayhty H, Sivonen A, et al. Haemophilus influenzae type b capsular polysaccharide vaccine in children: a double-blind field study of 100,000 vaccinees 3 months to 5 years of age in Finland. Pediatrics 1977;60:730-7.

- [5]. Robbins JB, Parke JC, Schneerson R. Quantitative measurement of “natural” and immunization-induced *Haemophilus influenzae* type b capsular polysaccharide antibodies. *Pediatr Res* 1973;7:103.
- [6]. Kayhty H, Peltola H, Kaanko V, et al. The protective level of serum antibodies to the capsular polysaccharide of *Haemophilus influenzae* type b. *J Infect Dis* 1983;147:1100.
- [7]. Anderson P. The protective level of serum antibodies to the capsular polysaccharide of *Haemophilus influenzae* type b. *J Infect Dis* 1984;149:1034.
- [8]. Makela PH, Peltola H, Kayhty H, et al. Polysaccharide vaccines of group A *Neisseria meningitidis* and *Haemophilus influenzae* type b: a field trial in Finland. *J Infect Dis* 1977;136:S43-S50.