Summary Basis for Regulatory Action

Date: January 14, 2016

From: Joseph J. Temenak, Ph.D., Chair of the Review Committee

BLA/ STN: 125347/231

Applicant Name: GlaxoSmithKline Biologicals

Date of Submission: March 16, 2015

PDUFA Goal Date: January 14, 2016

Proprietary Name/ Established Name: Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)/HIBERIX®

Additional Indication Proposed Under this Supplement: For active immunization for the prevention of invasive disease caused by Haemophilus influenzae type b. With this approval, Hiberix would be licensed for use in children for the primary series: One dose each at 2, 4, and 6 months of age. The first dose may be given as early as 6 weeks of age.

Recommended Action: Approval

Signatory Authority's Action: Approval

Office's Signatory Authority: Wellington Sun, M.D., Director, DVRPA

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.

Specific documentation used in developing the SBRA	Reviewer Name – Document Date
Clinical Review	Ralph LeBlanc, M.D., Ph.D. – January 14, 2016
Statistical Review (Clinical)	Ghideon Solomon, Ph.D. - November 14, 2015
Statistical Review (Serology Assays)	Rong Fu, Ph.D. - September 11, 2015
Epidemiology Review	David Menschik, M.D., M.P.H. - June 30, 2015
CMC/Product Review (Hep B Serology Assays)	Marian Major, Ph.D. - November 09, 2015
CMC/Product Review (Poliovirus Serology Assays)	Majid Laassri, Ph. D. - October 01, 2015
CMC/Product Review (Pertussis Serology Assays)	Rebecca Brady, Ph. D. - September 14, 2015
CMC/Product Review	Tina Roecklein, B.S. – November 23, 2015

Specific documentation used in developing the SBRA	Reviewer Name – Document Date
CMC/Product Review (Diphtheria and Tetanus Serology Assays)	Dianne Oram, Ph.D. - September 11, 2015
CMC/Product Review (Hib/Strep PS Serology Assays and Pneumo (b) (4))	Freyja Lynn, B.S. – July 24, 2015
Bioresearch Monitoring Review	Carla Jordan, BS, MT (ASCP), SBB - November 24, 2015
Advertising/Promotion Labeling	Sonny Saini, Pharm.D., M.B.A. - August 24, 2015

1. INTRODUCTION

Hiberix [*Haemophilus* b Conjugate Vaccine (Tetanus Toxoid Conjugate)] was approved under the Accelerated Approval regulations (21 CFR 601 Subpart E) in 2009 for active immunization as a booster dose in children 15 months through 4 years of age (prior to fifth birthday) for the prevention of invasive disease caused by *Haemophilus influenzae* type b. On March 16, 2015, GlaxoSmithKline (GSK) Biologicals (US License 1617) submitted this supplement to their Biologics License Application (BLA) to include safety and effectiveness data to support the use of Hiberix as a primary immunization series for active immunization of children 6 weeks to 14 months of age for the prevention of invasive disease caused by *Haemophilus influenzae* type b. Thus, with the current supplement's approval, Hiberix will be licensed for use in children 6 weeks through 4 years of age (prior to fifth birthday).

This efficacy supplement included data from study HIB-097, a multipurpose phase 3 study in infants and toddlers, which was intended 1) to provide data verifying the clinical benefit of Hiberix in children 15 months through 4 years of age in order to satisfy the requirements under Accelerated approval, and 2) to provide definitive data to support the approval of Hiberix as a primary immunization series in children 6 weeks to 14 months of age. Only the data related to the primary immunization series in younger children have been reviewed under this supplement, as discussed below. These data consist of a comparison of immunogenicity data across three lots of Hiberix and of Hiberix vs a US-licensed Hib vaccine, and relevant data regarding concomitant administration of Hiberix with other vaccines administered according to the US vaccination schedule.

2. BACKGROUND

GSK's HIBERIX® is a lyophilized vaccine containing 10 μg purified capsular polyribosylribitol phosphate (PRP) of Hib, covalently bound to Tetanus Toxoid (TT), per 0.5 mL dose. Since the initial launch in Germany in 1996, Hiberix has been licensed in 99 countries as a stand-alone vaccine and in over 100 countries when combined contemporaneously with other vaccines.

Hiberix was licensed in the US on August 19, 2009, for use as a booster dose in children age 15 months to 4 years old (prior to fifth birthday) for the prevention of invasive disease caused by *Haemophilus influenzae type b* (Hib) under the Accelerated Approval Regulations (21 CFR 601 Subpart E) to address the shortage of Hib vaccine in the US at that time.

To satisfy the requirement under accelerated approval of Hiberix for booster immunization, GSK conducted an adequate and well-controlled study to verify the clinical benefit of the vaccine by comparing the immune response induced by a booster immunization with Hiberix compared to two US-licensed Haemophilus b Conjugate Vaccines. GSK was also required to conduct a pediatric assessment of Hiberix in subjects ages 6 weeks to 14 months under the Pediatric Research Equity Act (PREA) (21USC 355c). GSK and CBER agreed that conducting the study Hib-097, which evaluated both the primary series and booster immunizations, could fulfill both, the accelerated approval as well as PREA requirements. However, CBER did not agree with GSK's proposal to submit a single efficacy supplement.

Instead, CBER requested the submission of 2 separate efficacy supplements as follows: 1) An efficacy supplement to include the data for the primary vaccine series in children 6 weeks to 14 months of age to satisfy the PREA requirement, and 2) An efficacy supplement to include the data for the booster vaccine dose in children 15 months to 4 years of age to confirm the clinical benefit of Hiberix in accordance with the requirements of accelerated approval of biological products regulations (21. CFR 601 40-46). The reason for the two separate supplements is that data derived from the confirmatory study required under the accelerated approval regulations cannot support extension of the indication to children less than 15 months of age. Therefore, data derived from study Hib-097on the primary vaccination of children 6 – 14 months of age would need to be submitted in a separate supplement.

With this efficacy supplement, GSK submitted revised labeling (PI, carton, vial) and the supporting clinical data from the portion of the single trial Hib-097 describing the primary immunization series of three doses administered to children at 2, 4, and 6 months of age and , if approved fulfilling the PREA post-marketing requirement.

3. CHEMISTRY MANUFACTURING and CONTROL (CMC) AND CLINICAL SEROLOGICAL ASSAY INFORMATION

Hiberix product formulation (per 0.5 mL dose) is as follows: Active ingredient: 10 ug purified capsular polyribosylribitol phosphate (PRP) of Hib conjugated to ~25 ug TT (tetanus toxoid). The excipient lactose (12.6 mg per dose) is used as a stabilizer. GSK confirmed that no changes were implemented for the manufacturing of the clinical lots used in study Hib-097 compared to the manufacturing process described in the BLA.

Documentation of assay performance was provided for measurement of the immune responses to Hib (PRP) and to antigens contained in other vaccines administered concomitantly. For the (b) (4) use to measure antibodies to PRP, diphtheria toxoid, tetanus toxoid, pertussis antigens (PT, FHA, PRN) and pneumococcal polysaccharides documentation included validation reports, SOPs, assay stability data and clinical data line listings. No assay performance issues or aberrant assay data were noted at the time of initial testing upon completion of study Hib-097 (primary series portion) in November 2012, GSK has since begun a revalidation program, and is working in close cooperation with CBER to update and/or modernize their current assays. Overall, the assays are considered adequate for their intended use in study Hib-097 for the following reasons: 1) the lack of any data that would indicate that the assays were not performing adequately, 2) the absence of any indication that the assays are unstable, 3) the absence of any data in the study that are unusual or anomalous, and 4) the internally controlled design of the

study. The poliovirus neutralization assay was validated in 1998, and is performed according to WHO guidelines. GSK provided additional information to demonstrate assay performance stability between 2002 and 2013, and CBER concluded that the poliovirus neutralization assay appears to be fit for the purpose of determining poliovirus sero-responses in study Hib-097.

The assay for quantitation of antibodies to hepatitis B surface antigen (HBs, in-house (b) (4) was validated in 2006. In 2012, this in-house assay was found to have a specificity issue characterized by overestimation of antibody concentrations in the low range (b) (4)). The investigations and associated data were submitted under IND 2846, Amendment 183 (Engerix-B) on December 20, 2013. The investigation indicated that the results of previous clinical trials (to include the Hib-097 study) were not impacted by the specificity issue with the anti-HBs (b) (4)

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

Given the extent of human experience with Hiberix, non-clinical data were not required and no new non-clinical data was submitted to support this sBLA.

5. CLINICAL PHARMACOLOGY/PHARMACOVIGILANCE

An updated version of the Pharmacovigilance plan was submitted in the efficacy supplement to include the results from study Hib-097. A recommendation was made to the sponsor, and accepted, to include the preferred terms 'cyanosis', 'hypotonia', and 'pallor' in the post-marketing experience section of the prescribing information (PI). The sponsor's revised pharmacovigilance plan was determined to be adequate. Post-marketing adverse experiences will be reported to CBER in accordance with 21 CFR 600.80, and distribution reports provided to CBER in accordance with 21 CFR 600.81. No safety PMR or REMS is required at this time.

6. CLINICAL/ STATISTICAL

Prior to the initiation of study Hib-097 GSK consulted with CBER to reach agreement on the study design and endpoints. HIB-097 was initiated on 18-June-2010 and completed on 17-July-2013 and was conducted at 67 sites in the United States under US IND 14151. It was a Phase III, randomized, multicenter study and double-blinded for the immunogenicity and consistency evaluation of 3 lots of Hiberix, single-blinded and controlled for the evaluation of the safety and immunogenicity of Hiberix compared to ActHIB, a monovalent Hib vaccine [Sanofi Pasteur, Inc.] and open-label for the comparison of the immunogenicity of Hiberix with Pentacel, a combination DTPa-IPV-HIB vaccine[Sanofi Pasteur, Inc.]. The study vaccines were administered to healthy infants at 2, 4, 6 and 15-18 months of age with recommended pediatric vaccines co-administered at separate sites.

Specifically, there were five treatment groups, three investigational and two active controls, randomized on a 2:2:2:1:1 basis, with 3,552 of 4003 vaccinated subjects who completed the full study, per protocol. The Investigational Groups were: Groups Hiberix A, Hiberix B and Hiberix C: [subjects received 3 doses of Hiberix at 2, 4 and 6 months by lot, co-administered with 3 doses of Pediarix (DTPa-IPV-HepB) and Prevnar13 (13 valent pneumococcal) and 2 doses of Rotarix (Rotavirus. Live, oral)]; and the Active Control Groups were: Group ActHIB: (subjects received 3 doses of ActHIB at 2, 4 and 6

months co-administered with 3 doses of Pediarix and Prevnar13 and 2 doses of Rotarix) and Group Pentacel [subjects received 3 doses of Pentacel at 2, 4 and 6 months co-administered with 3 doses of Prevnar13, 3 doses of Engerix-B (Hepatitis B) and 2 doses of Rotarix].

HIB-097 had seven co-primary endpoints to address a) lot to lot consistency of three lots of Hiberix; b) non-inferiority of Hiberix compared to ActHIB one month after each of 3 primary vaccine doses at ages 2, 4 and 6 months using anti-PRP antibody concentration ≥ 1.0/ug/mL and ≥0.15ug/mL; and c) non-inferiority of immune responses to co-administered antigens: diphtheria (D) and tetanus (T), pertussis toxoid (PT), filamentous hemagglutinin (FHA), pertactin (PRN), poliovirus types 1,2 and 3, and thirteen serotypes of *S. pneumoniae*. Of note, previous studies, using both conjugated and un-conjugated HIB vaccines produced by other manufacturers, and cited in the scientific literature, to evaluate the relationship between anti-PRP antibody levels to protect infants from invasive Hib disease, established that a minimum anti-PRP level of ≥ 0.15ug/mL was necessary for protection from invasive disease and that levels ≥ 1.0ug/mL correlated with protection from invasive disease for up to one year post primary series.

Lot to lot consistency results: Table 1 shows the results of the lot to lot consistency analysis.

Hiberix Study group			**Hiberix Study group**			**GMC ratio**		**95% CI for the GMC ratio**	
	N	**Anti-PRP GMC**		**N**	**Anti-PRP GMC**		**Value**	**LL**	**UL**
Hiberix Lot A	527	4.994	*Hiberix* Lot B	537	6.323	*Hiberix* Lot A / *Hiberix* Lot B	0.790	**0.641**	**0.974**
Hiberix Lot A	527	4.994	*Hiberix* Lot C	526	4.416	*Hiberix* Lot A / *Hiberix* Lot C	1.131	**0.916**	**1.396**
Hiberix Lot B	537	6.323	*Hiberix* Lot C	526	4.416	*Hiberix* Lot B / *Hiberix* Lot C	1.432	**1.161**	**1.765**

Source: adapted from sBLA 125347.231, CSR HIB-097, table 55, p. 219
GMC = geometric mean antibody concentration
N = Number of subjects with post-vaccination results available
95% CI = 95% confidence interval for the GMC ratio (ANOVA model - pooled variance of the three groups in the comparison); LL = lower limit, UL = upper limit
Lot equivalence criteria: The criterion for lot-to-lot consistency was that the two-sided 95% confidence limits on the anti-PRP GMC ratio between lots were within the [0.67; 1.5] interval for all 3 pair-wise comparisons.

Statistical analyses of the primary objectives were specified to be performed in a hierarchal manner, as follows: lot to lot consistency of three lots of Hiberix; non-inferiority of Hiberix compared to ActHIB one month after the 3rd vaccination in the primary series in terms of anti-PRP antibody concentration ≥ 1.0/ug/mL and ≥0.15ug/mL; and the non-inferiority of Hiberix to ActHIB on the immune responses

elicited to antigens contained in co-administered vaccines (diphtheria and tetanus, pertussis toxoid (PT), filamentous hemagglutinin (FHA), pertactin (PRN), poliovirus types 1,2 and 3, and thirteen pneumococcal serotypes).

Data in table 1 show that the first co-primary endpoint with regard to lot-to-lot consistency was not met due to the higher GMC for Lot B, which resulted in the 95% CI for the LL of the ratio between Lot A to Lot B to be 0.64 [less than the 0.67 LL criteria]. Since the statistical analysis plan was hierarchical in nature, failure to meet this first co-primary endpoint would indicate that further analysis of co-primary endpoints could not be conducted. However, the narrow margin by which the statistical lot consistency criterion was missed is not deemed to be clinically significant. Therefore, the subsequent analyses of anti-PRP antibody levels and antibody levels induced by co-administered routine childhood vaccine antigens was allowed to proceed because the immune responses induced by Hiberix Lots A, B and C were found to be unlikely to result in clinically meaningful differences and the GMC titers obtained for each lot were deemed to be sufficient to induce protection from invasive Hib disease. No immune interferences with co-administered antigens were observed, and the safety profile appears acceptable and similar to two US-licensed Hib vaccines."

Non-inferiority of Hiberix compared to ActHIB: The second and third co-primary endpoints were to demonstrate the non-inferiority of Hiberix to ActHIB, each co-administered with Pediarix, Prevnar13 and Rotarix, following 3 primary vaccine doses using anti-PRP antibody concentration of ≥ 1.0/ug/mL (co-primary endpoint 2) and ≥0.15 ug/mL (co-primary endpoint 3). The criteria for non-inferiority (1 month after the last dose of the primary vaccinations series at 2, 4 and 6 months) were as follows: the lower limit of the standardized asymptotic 95% CI for the difference (pooled Sub-cohorts Hiberix A-PRP, Hiberix B-PRP and Hiberix C-PRP minus Subcohort ActHIB) in the percentage of subjects with anti-PRP concentrations ≥1.0 ug/mL was ≥-10%. For anti-PRP concentrations ≥0.15 ug/mL the lower limit of 95% CI was ≥- 5%.

The difference in the percentage of subjects with anti-PRP concentrations ≥1.0 ug/mL between the Hiberix and ActHIB groups (Hiberix minus ActHIB) was - 8.59% with a 95% LL CI of -12.28 and therefore, this co-primary endpoint was not met. In the Hiberix group, 81.2% of subjects achieved anti-PRP concentrations of ≥1.0 ug/mL and 89.8% achieved ≥1.0 ug/mL in the ActHIB group.

The difference in the percentage of subjects with anti-PRP concentrations ≥0.15 ug/mL between the Hiberix and ActHIB groups (Hiberix minus ActHIB) was -0.11% with a 95% LL CI of -1.98 and therefore, this co-primary endpoint was met. In the Hiberix group, 96.6% of subjects achieved anti-PRP concentrations of ≥0.15 ug/mL and 96.7% achieved 0.15 ug/mL in the ActHIB group. While the percentage of subjects in the Hiberix group with anti-PRP Ab titers ≥ 1.0ug/mL one month after the primary series [81.2%] was less than that in the ActHIB group [89.8%] at approximately 7 months of age, by 14 months of age these percentages were similar between these two groups [Hiberix, 32.2% and ActHIB 27.0%] and by 16 months of age, one month post booster dose, 99.1% of Hiberix subjects and 97.9% of ActHIB subjects achieved anti-PRP Ab titers ≥ 1.0ug/mL.

Of note, there was a second active comparator U.S. licensed HIB vaccine, Pentacel [DTaP-IPV-Hib] included in study Hib-097 consisting of an equal number of subjects as enrolled in the ActHIB group [N=520]. Although not pre-specified as a co-primary objective the percentage of male subjects who achieved an anti-PRP antibody concentration ≥0.15ug/ml one month after primary series was 96.2% for Hiberix and 90.4% for Pentacel; and the percentage of male subjects who achieved ≥1.0ug/ml anti-PRP antibody titer one month after primary series was 79.4% for Hiberix and 75% for Pentacel. The comparisons were very similar for female subjects. Even though the comparison of anti-PRP antibody results between Hiberix and Pentacel was exploratory it can be viewed as supportive data.

It is concluded, taking into account the totality of the immunogenicity data from this study, that a primary vaccination series of Hiberix to children 2, 4 and 6 months of age, induces an immune response likely to protect from invasive *Haemophilus influenzae* type b disease during the interval from age 2 months to the recommended booster dose at age 15 months [15 months to 4 years of age].

Non-inferiority of immune responses to co-administered antigens:
Study HIB-097 had four co-primary endpoints to evaluate the immune responses to co-administered antigens [diphtheria, tetanus, pertussis, polio 1, 2, and 3 and thirteen serotypes of *S. pneumoniae*]. Hiberix or ActHIB (primary series) were co- administered with Pediarix (DTaP- IPV-HepB), Prevnar 13 and Rotarix to children aged 2, 4 and 6 months. The results showed that Hiberix was non-inferior to ActHIB in comparisons of anti-diphtheria and anti-tetanus antibodies with both vaccines demonstrating that 100% of subjects achieved anti-D and anti T titers greater than the seroprotective value of 0.1IU/mL when they were co-administered with Pediarix. The comparisons of antibodies to each of the pertussis antigens, PT, FHA and PRN demonstrated that the LL of the 97.5% CIs for anti-PT, anti-FHA and anti-PRN all exceeded 0.9 which was greater than the 0.67 limit for clinical non-inferiority. The comparison of percentage of subjects with seroprotective titers ≥8 to each of the poliovirus antigens demonstrated that seroprotective titers (≥8) of antibodies to each of the poliovirus antigens was 96.8, 95.5 and 96.3 for anti-Polio 1, 2 and 3, respectively, and thus met the criteria for non-inferiority. Finally, for each *S. pneumoniae* serotype (1 [anti-1], 3 [anti-3], 4 [anti-4], 5 [anti-5], 6A [anti-6A], 6B [anti-6B], 7F [anti-7F], 9V [anti-9V], 14 [anti-14], 18C [anti-18C], 19A [anti-19A], 19F [anti-19F] and 23F [anti-23F]) , the LL of the 97.5% CI on the GMC ratios was at least 0.8 which were greater that the criteria of ≥ 0.5 (clinical limit for non-inferiority). Data showed that Hiberix did not interfere with the immune responses to the diphtheria, tetanus, pertussis, polio or *S. pneumoniae* antigens.

Of note, the statistical review concluded that "while the clinical study results did not meet the predefined statistical criteria for lot consistency and non-inferiority of Hiberix to ActHIB, the overall data generated in this study indicate that the consistency of the immune response in terms of GMCs were within observed variability of two US-licensed Hib vaccines, and non-inferiority criteria were met versus Pentacel, a US-licensed Hib vaccine. Furthermore, non-inferiority to ActHIB was observed at the 0.15 mcg/mL threshold

CBER Bioresearch Monitoring (BIMO) issued inspection assignments, i.e., four of the 63 clinical sites with enrolled subjects were selected for inspection as follows: 1) Pediatric

Associates of Fall River, Fall River, Massachusetts, 2) Palmetto Pediatrics, N. Charleston, SC, 3) Central Arkansas Pediatrics, Benton, Arkansas, and 4) Kaiser Permanente Vaccine Study Center, Oakland, California. These sites represented approximately 22% of the subjects enrolled in this study. The inspections did not reveal significant problems that impacted the data submitted in this marketing application.

Pediatric Research Equity Act (PREA)

Hiberix was discussed during the Pediatric Review Committee (PeRC) meeting on November 18, 2015. The committee concurred with Office of Vaccine Research and Review's (OVRR's) assessment that Hiberix Study-097 fulfilled the pediatric study requirement in children 6 weeks to 4 years of age. The PeRC also agreed that Hiberix given to infants from 0 to <6 weeks of age does not represent a meaningful therapeutic benefit over initiating vaccination at 6 weeks of age as the vaccine is unlikely to elicit significant immune response in this age group and would not likely to be used in a substantial number of pediatric patients this age. Therefore, a study in this age group was waived Similarly, PeRC agreed to continue the waiver for study of Hiberix in children 5 to 17 years of age for multiple reasons: The risk of invasive disease due to *Haemophilus influenzae type b* is generally negligible in this older age group and thus, does not represent a meaningful therapeutic benefit over vaccination at younger ages, and the necessary studies are impossible or highly impracticable because the number of unimmunized children 5 to 17 years of age who have underlying medical conditions that may predispose them to invasive disease due to *Haemophilus influenzae type b* is limited, and such children would be geographically dispersed. Thus, with Study HIB-097 the applicant has completed all requirements for pediatric assessment under PREA.

7. SAFETY

Safety data derived from 3,552 of 4003 vaccinated subjects who completed the study through visit 4, one month after the primary vaccination series of three immunizations at 2,4 and 6 months of age were reviewed. The most common solicited local adverse event was pain with 7-13% of all subjects having Grade 3 [Severe: Cried when limb was moved/spontaneously painful]. Irritability was the most common solicited general adverse event and grade 3 fever [≥39.5C, rectal] was reported for 0.4-1.4% of subjects. Upper Respiratory Tract Infection [URTI], cough and otitis media were the most frequently reported unsolicited general adverse events. New Onset of Chronic Diseases [NOCDs] were observed and the most common ones reported were atopic dermatitis, asthma and eczema at rates of ≤1.2% each in each of the groups, Hiberix, ActHIB and Pentacel. No deaths were reported in the study.

Serious Adverse Events [SAEs] were reported in 3.6% of subjects in the Hiberix group; 4.6% in the ActHIB group; and 4.0% in the Pentacel group. Five SAEs were classified as related to the investigational product by the investigator: single cases of normal sleep myoclonus, of Kawasaki Disease, of afebrile seizure and of involuntary muscle contraction of one leg were each reported for the Hiberix group and each resolved by the end of the primary epoch which was one month after the third dose of vaccine was administered. One case of possible seizure in the ActHIB group was reported. CBER requested that the GSK medical team review the likely causality of the Kawasaki's Disease and involuntary muscle contractions SAEs as part of the label review. GSK determined that these two SAEs were not likely to be related to vaccine administration and deleted these from the proposed label in agreement with CBER. In summary, the

safety data demonstrates primarily mild, local and systemic adverse reactions at rates that are within the range observed for most pediatric age vaccines, with no significant discrepancies in rates between the Hiberix, ActHIB and Pentacel groups and no safety signals were detected.

Special Populations and Demographic Groups: Gender was balanced for each of the three HIB vaccine groups. Sixty (60%) of enrolled subjects were ethnically classified as "White" , 9-10% were African-Americans, 8% were American Indian or Alaskan Native , and 7% were any Asian . Immune response parameters were reported by sex and by race (white or other). Anti-PRP levels at the ≥1.0ug/mL were generally higher for females compared to males and higher for the classification "other" compared to "white"; however, the magnitude of these differences were not likely to be clinically significant. No such differences were reported for anti-PRP antibodies at the ≥0.15ug/mL level. There were no significant differences by race or by sex for anti-D or anti-T sero-response rates or percentage of subjects achieving titers of ≥0.1IU/mL or ≥1.0IU/mL.

8. ADVISORY COMMITTEE MEETING

The application was not referred to the Vaccines and Related Biological Products Advisory Committee because the review of information submitted in this supplement did not raise concerns or controversial issues which would have benefited from an advisory committee discussion.

9. OTHER RELEVANT REGULATORY ISSUES

No additional relevant issues.

10. LABELING

Review of the revised prescribing information (PI) identified deficiencies, which required modifications to the text. In addition, revisions to the container label and carton were also made under this supplement. After negotiations with the sponsor, it was determined by the committee that the PI for Hiberix is acceptable. The following changes were made to the label; under "Indications and Usage" the label now states "approved for use in children 6 weeks through 4 years of age (prior to fifth birthday)."; under "Warnings and Precautions" a statement concerning apnea in premature infants following IM vaccination has been added; and the immunogenicity and safety data from Study HIB-097 were added to the label.

11. RECOMMENDATIONS AND RISK/BENEFIT ASSESSMENT

The committee recommends approval of this sBLA to include safety and effectiveness data to support the use of Hiberix for active immunization for the prevention of invasive disease caused by *Haemophilus influenzae* type b in children 6 weeks to 14 months of age, revisions to product labeling and an updated Pharmacovigilance Plan.