DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Division of Biostatistics

STATISTICAL REVIEW AND EVALUATION

BLA

BLA/Supplement Number:	125347/0
Product Name:	Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)
Indication(s):	Active immunization against *Haemophilus influenzae* type b starting from 6 weeks of age as a 3-dose primary series with a single booster given at 15 to 18 months
Applicant:	GlaxoSmithKline (GSK) Biologicals
Date(s):	March 17, 2009
Review Priority:	Priority
Statistical Branch:	CBER/OBE/DB/VEB
Primary Statistical Reviewer:	Ghideon Ghebregiorgis, Ph.D. Reviewer's name _____ Date
Concurring Reviewer (1):	Tammy Massie, Ph.D. First concurring reviewer's name _____ Date
Concurring Reviewer (2):	A. Dale Horne, Dr.P.H Second concurring reviewer's name _____ Date
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Table of Contents

1. EXECUTIVE SUMMARY 3

2. STUDY HIB-097 3

2.1 STUDY OBJECTIVES 3
2.2 STUDY DESIGN 8
2.3 STATISTICAL EVALUATION 10
2.4 REVIEWER'S COMMENTS 13

3. STUDY DTPA-IPV-026 14

3.1 STUDY OBJECTIVES 14
3.2 STUDY DESIGN 15
3.3 STATISTICAL EVALUATION 15
3.4 REVIEWER'S COMMENTS 20

4. STUDY DTPA-HBV-032 22

4.1 STUDY OBJECTIVIES 22
4.2 STUDY DESIGN 22
4.3 STATISTICAL EVALUATIONS 23
4.4 REVIEWER'S COMMENTS 25

5. STUDY DTPA-HBV-020 25

5.1 STUDY OBJECTIVES 26
5.2 STUDY DESIGN 26
4.3 STATISTICAL EVALUATIONS 27
4.4 REVIEWER'S COMMENTS 28

6. STUDY DTPA-IPV-013P 28

6.1 STUDY OBJECTIVES 28
6.2 STUDY DESIGN 29
6.3 STATISTICAL EVALUATIONS 29
6.4 REVIEWER'S COMMENTS 30

7. STUDY DTPA-HBV-IPV-028 30

7.1 STUDY OBJECTIVES 30
7.2 STUDY DESIGN 31
7.3 STATISTICAL EVALUATIONS 31
7.4 REVIEWER'S COMMENTS 32

8. STUDY DTPA-HBV-IPV-010 33

8.1 STUDY OBJECTIVES 33
8.2 STUDY DESIGN 33
8.3 STATISTICAL EVALUATIONS 33
8.4 REVIEWER'S COMMENTS 35

9. STUDY DTPA-HBV-IPV-035 36

9.1 STUDY OBJECTIVES 36
9.2 STUDY DESIGN 36
9.3 STATISTICAL EVALUATIONS 37
9.4 REVIEWER'S COMMENTS 39

10. CONCLUSIONS AND RECOMMENDATIONS 47

1. Executive summary

GSK submitted this application for licensure of *Hiberix* (GSK's lyophilized vaccine of purified polyribosyl-ribitol-phosphate capsular polysaccharide (PRP) of Hib covalently bound to inactivated tetanus toxoid) for a booster immunization (4th dose vaccination) against invasive diseases caused by *Haemophilus influenzae* type b in the US under accelerated approval regulations. Hiberix was first licensed in Germany in 1996 and currently is licensed in 100 different counties.

GSK is requesting the approval of this submission (licensure of Hiberix as a booster dose) based on seven studies conducted in Europe, Canada, and Latin America. The safety and reactogenicity profile of Hiberix administered as a 4th dose vaccination were evaluated in all of the seven studies submitted. Immunogenicity was evaluated in all studies except one (DTPa-HBV-IPV-028). The applicant claims the data generated by these six studies support the safety and immunogenicity of Hiberix when administered as a booster vaccination.

The plans for the studies included in this BLA were not provided to the FDA prior to study creation or during the implementation of the study. Had the study protocols been submitted under IND, CBER would have conveyed the comments included at the end of each study summary included within this review.

GSK included the following note at the beginning of each of the seven modified study reports included in this BLA: "*There was no statistician review for this modified (Hiberix BLA only) report as the analyses section of the original report were reviewed and agreed upon by the statistician. No new data were generated and existing data were not modified*".

Considering the lack of opportunity to provide feedback and suggestions to the applicant's proposed study, many of these studies provided within STN 125347 still appear to support the applicant's claim that this product appears to be safe and to elicit adequate immune response. The summary table below provides the safety and immunogenicity results that support this conclusion.

Study No	Immunogenicity	Safety
DTPa-IPV- 026	Yes (at east 86.7% of subjects were seropositive)	Yes (1 serious adverse event unrelated to vaccine, no discontinuations due to AEs or SAEs)
DTPa-HBV-032	Yes (all subjects had anti-PRP titer ≥ 0.15 mcg/ml)	Yes (76 unsolicited AEs, 9 of which were considered probably or suspected to be vaccine related, No SAE)
DTPa-HBV-020	Yes(all subjects reached anti-PRP antibody titer concentration of 1.0 mcg/ml)	Yes (redness (22.7%) was the most frequently reported local symptom and fever (28.9%) was the most frequent general symptom)
DTPa-IPV-013p	Yes (all subjects had anti-PRP titer $\geq 0.15\ \mu g/ml$)	Yes (all symptoms reported were mild to moderate in intensity)
DTPa-HBV-IPV-028	NA	Yes (12.8% grade 3 solicited symptoms, 2 subjects report SAEs assessed as unrelated to vaccination)
DTPa-HBV-IPV-010	Yes (>64% of subjects were seropositive)	Yes (14 local and 30 general symptoms reported)

DTPa-HBV-IPV-035	Yes (96.4% of subjects had anti-PRP antibody concentration ≥ 1.0 mcg/ml	Yes (No SAEs were reported. 92 local, 104 general and 119 any symptoms (solicited and unsolicited) reported).

1.1 Overview

This statistical review covers 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.

2. Study HIB-097 (112957)

This section contains a statistical review for the concept protocol proposed by GSK for a confirmatory study to evaluate consistency and immunogenicity of 3 lots of GSK Biologicals Hib vaccine 208108 versus *ActHIB* and *Pentacel* at 2, 4, 6, and 15-18 months of age in healthy infants.

Per the sponsor, the study is "a primary and booster phase III, randomized, double-blinded for the immunogenicity and consistency evaluation of 3 GSK Biologicals' *Haemophilus influenzae* type b (Hib) vaccine lots and single blinded and controlled for the evaluation of safety and immunogenicity of GSK Biologicals' Hib vaccine compared to a monovalent Hib vaccine and open for comparison with a combined DTaP-IPV-Hib vaccine when administered to healthy infants at 2, 4, 6 and 15-18 months of age with recommended co-administrations but at separate sites."

2.1 Study Objectives:

Within study HIB-0097 (112957), successful outcome is achieved only if the statistical criterion for the first objective (lot-to-lot consistency) as well as all the criteria for the seven co-primary objectives are met.

Co-primary objectives (primary vaccine phase):

- To demonstrate the lot-to-lot consistency of 3 manufacturing lots of *Hiberix* co-administered with *Pediarix*, *Prevnar,* and *Rotarix* following 3 primary doses in terms of immune response to polyribosylribitol phosphate (PRP)

Criteria for lot-to-lot consistency:
Lot-to-lot consistency will be achieved if the two-sided 95% confidence bounds on the anti-PRP geometric mean concentrations (GMC) ratio between lots are within the [0.5; 2.0] interval.

Reviewer's comment:
For lot-to-lot consistency CBER recommends a pair-wise comparison of the 95% CI on the ratio of GMC's for anti-PRP formed by the 3 lots; the two-sided 95% CI on the GMC ratio should be entirely within 0.67 and 1.5. (GSK agreed to use the recommended interval in a response dated May 15th, 2009).

- To demonstrate the non-inferiority of *Hiberix* to *ActHIB*, each co-administered with *Pediarix, Prevnar,* and *Rotarix*, following 3 primary doses in terms of immune response to PRP.

Criterion for non-inferiority (1 month after last dose of primary vaccination):

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 Sub-cohort ActHIB-PRP) in the percentage of subjects with anti-PRP concentrations ≥1.0 µg/ml is ≥-10%.

- To demonstrate the non-inferiority of *Hiberix* co-administered with *Pediarix*, *Prevnar,* and *Rotarix* to *Pentacel* co-administered with *Prevnar, Rotarix,* and *Engerix-B*, following 3 primary doses in terms of immune response to PRP.

Criterion for non-inferiority (1 month after last dose of primary vaccination):
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 Sub-cohort Pentacel-PRP) in the percentage of subjects with anti-PRP concentrations ≥1.0 µg/ml is ≥-10%.

- To demonstrate the immunological non-inferiority of *Pediarix* co-administered with *Hiberix*, *Prevnar,* and *Rotarix* to *Pediarix* co-administered with *ActHIB, Prevnar,* and *Rotarix*, following 3 primary doses.

Criteria for non-inferiority (1 month after last dose of primary vaccination):

Lower limits of the standardized asymptotic 95% CIs on the differences (Sub-cohort Hiberix-CoAd minus Sub-cohort ActHIB-CoAd) in the percentages of subjects with seroprotective concentrations (≥0.1 IU/ml) of anti-diphtheria and anti-tetanus antibodies are ≥-10%

and

Lower limits of the 95% CIs on the GMC ratios (Sub-cohort Hiberix-CoAd divided by Sub-cohort ActHIB-CoAd) for antibodies to each of the pertussis antigens (pertussis toxoid [PT], filamentous hemagglutinin [FHA], and pertactin [PRN]) are ≥0.67

and

Lower limits of the standardized asymptotic 95% CIs on the differences (Sub-cohort Hiberix-CoAd minus Sub-cohort ActHIB-CoAd) in the percentages of subjects with seroprotective titers (≥8 dil^{-1}) of antibodies to each of the poliovirus antigens are ≥-10%.

- To demonstrate the immunological non-inferiority of *Prevnar* co-administered with *Hiberix*, *Pediarix,* and *Rotarix* to *Prevnar* co-administered with *ActHIB, Pediarix,* and *Rotarix*, following 3 primary doses.

Criteria for non-inferiority (1 month after last dose of primary vaccination):
Lower limits of the two-sided 95% CI on the GMC ratio (Sub-cohort Hiberix-CoAd over Sub-cohort ActHIB-CoAd) for each S. pneumoniae serotype (4 [anti-4], 6B [anti-6B], 9V [anti-9V], 14 [anti-14], 18C [anti-18C], 19F [anti-19F] and 23F [anti-23F] are ≥0.5.

Reviewer's comment: The recommended lower limit of the two-sided 95% CI is 0.67.

Secondary objectives (Primary vaccination phase):

Immunogenicity

- To describe the immunogenicity of 3 manufacturing lots of *Hiberix* following 3 primary doses in terms of the percentage of subjects with anti-PRP concentrations ≥0.15 μg/ml and ≥1.0 μg/ml, and in terms of anti-PRP GMCs.

- To evaluate the immunogenicity of a 3-dose primary vaccination course of *Hiberix* co-administered with *Prevnar, Rotarix,* and *Pediarix* compared to that of *ActHIB,* co-administered with *Prevnar, Rotarix,* and *Pediarix* and to that of *Pentacel* co-administered with *Prevnar, Rotarix,* and *Engerix-B* in terms of anti-PRP concentrations ≥0.15 μg/ml, ≥1.0 μg/ml, and in terms of anti-PRP GMCs.

- To explore the non-inferiority of *Hiberix* to *ActHIB*, each co-administered with *Pediarix, Prevnar,* and *Rotarix*, and to *Pentacel*, co-administered with *Engerix*, *Prevnar,* and *Rotarix*, following 3 primary doses in terms of immune response to PRP.

Criterion for non-inferiority (1 month after last dose of primary vaccination):
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 Sub-cohort ActHIB-PRP or Sub-cohort Pentacel-PRP) in the percentage of subjects with anti-PRP concentrations ≥0.15 μg/ml is ≥-10%.

- To explore the superiority of *Hiberix* co-administered with *Pediarix, Rotarix,* and *Prevnar* to *Pentacel* co-administered with *Prevnar, Rotarix,* and *Engerix-B*, following 3 primary doses in terms of the percentage of subjects with anti-PRP concentrations ≥0.15 μg/ml, ≥1.0 μg/ml, and in terms of anti-PRP GMCs.

This objective will only be assessed if the third co-primary objective of non-inferiority of Hiberix to Pentacel is met.

- To evaluate the immunogenicity of a 3-dose primary vaccination course of *Pediarix* co-administered with *Hiberix, Rotarix,* and *Prevnar* compared to that of *Pediarix* co-administered with *ActHIB, Rotarix,* and *Prevnar* and to that of *Pentacel* co-administered with *Prevnar, Rotarix,* and *Engerix-B* with respect to diphtheria, tetanus, PT, FHA, PRN, hepatitis B, and poliovirus types 1, 2, and 3 (except for the evaluations specified in the primary objectives).

- To evaluate the immunogenicity of a 2-dose primary vaccination course of *Rotarix* co-administered with *Pediarix*, *Hiberix,* and *Prevnar* compared to that of *Rotarix* co-administered with *Pediarix, ActHIB,* and *Prevnar* and to that of *Rotarix* co-administered with *Pentacel*, *Prevnar,* and *Engerix-B* in terms of anti-rotavirus antibody concentrations ≥20 U/ml.

- To evaluate the immunogenicity of a 3-dose primary vaccination course of *Prevnar* co-administered with *Hiberix, Rotarix,* and *Pediarix* compared to that of *Prevnar* co-administered with *ActHIB, Rotarix,* and *Pediarix* and to that of *Prevnar* co-administered with *Pentacel, Rotarix,* and *Engerix-B* in terms of *S.pneumoniae*, GMCs, and antibody concentrations ≥0.05 μg/ml, ≥0.2 μg/ml, and ≥0.5 μg/ml for the seven serotypes in *Prevnar*.

Safety

Within study HIB-0097 (112957), the objectives of the study include examination and comparisons of the safety and reactogenicity of ActHIB including:

- To evaluate the safety and reactogenicity of a 3-dose primary vaccination course of *Hiberix* co-administered with *Pediarix, Rotarix,* and *Prevnar* compared to that of *ActHIB* co-administered with *Pediarix, Rotarix,* and *Prevnar* and to that of *Pentacel* co-administered with *Prevnar, Rotarix,* and *Engerix-B*.

- To explore the equivalence of the safety of *Hiberix* co-administered with *Pediarix, Rotarix,* and *Prevnar* to that of *ActHIB* co-administered with *Pediarix, Rotarix,* and *Prevnar* with respect to the incidence of any grade 3 symptom (solicited or unsolicited) within 4 days (Day 0 to Day 3) after any vaccine dose.

Co-primary objectives (Booster vaccine phase):

Within the Booster vaccine phase of study HIB-0097 (112957), the co-primary objectives include:

- To demonstrate the immunological non-inferiority of a booster dose of *Hiberix* co-administered with *Infanrix* in subjects 15-18 months of age who received 3 primary vaccine doses of *Hiberix* compared to that of a booster dose of *ActHIB* co-administered with *Infanrix* in subjects 15-18 months of age who received 3 primary vaccine doses of *ActHIB* in terms of immune response to PRP.

Criterion for non-inferiority (1 month after the booster vaccination):
Lower limit of the two-sided standardized asymptotic 95% CI on the difference (Sub-cohort Hiberix-Inf minus Sub-cohort (booster) ActHIB) in the percentage of subjects with anti-PRP concentration ≥1.0 μg/ml is ≥ -10%.

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

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

and

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

and

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

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

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

Secondary objectives (Booster vaccination phase (+persistence)):

Immunogenicity

- To evaluate, prior to the administration of a booster dose of *Hiberix*, *ActHIB,* or *Pentacel* at 15-18 months of age, the persistence of the anti-PRP antibodies induced by three

primary doses of *Hiberix*, *ActHIB*, each co-administered with *Pediarix* and *Prevnar* and *Rotarix*, or Pentacel co-administered with *Engerix-B, Rotarix,* and *Prevnar*.

- To evaluate, prior to the administration of a booster dose of Hib vaccine at 15-18 months of age, the persistence of the anti-HBs and anti-poliovirus 1, 2, 3 antibodies induced by *Pediarix* or *Pentacel/Engerix-B* in subjects of the Sub-cohort Hiberix-CoAd and the Sub-cohort Pentacel- CoAd.
- To evaluate the immunogenicity of a booster dose of *Hiberix* co-administered with *Infanrix*, *Hiberix* co-administered with *Kinrix, ActHIB* co-administered with *Infanrix* and *Pentacel* in terms of the percentage of subjects with anti-PRP concentrations ≥0.15µg/ml, ≥1.0 µg/ml and GMCs one month after the booster dose.
- To evaluate the immunogenicity of a booster dose of *Infanrix* co-administered with *Hiberix*, *-------b(4)----------, Infanrix* co-administered with *ActHIB* and *Pentacel* with respect to diphtheria, tetanus, PT, FHA, and PRN antibodies.
- ----------b(4)----------

Safety

- To evaluate the safety and reactogenicity of a booster dose of *Hiberix* co-administered with *Infanrix, Hiberix* co-administered with *Kinrix*, *ActHIB* co-administered with *Infanrix* and *Pentacel,* at 15-18 months.

2.2 Study design

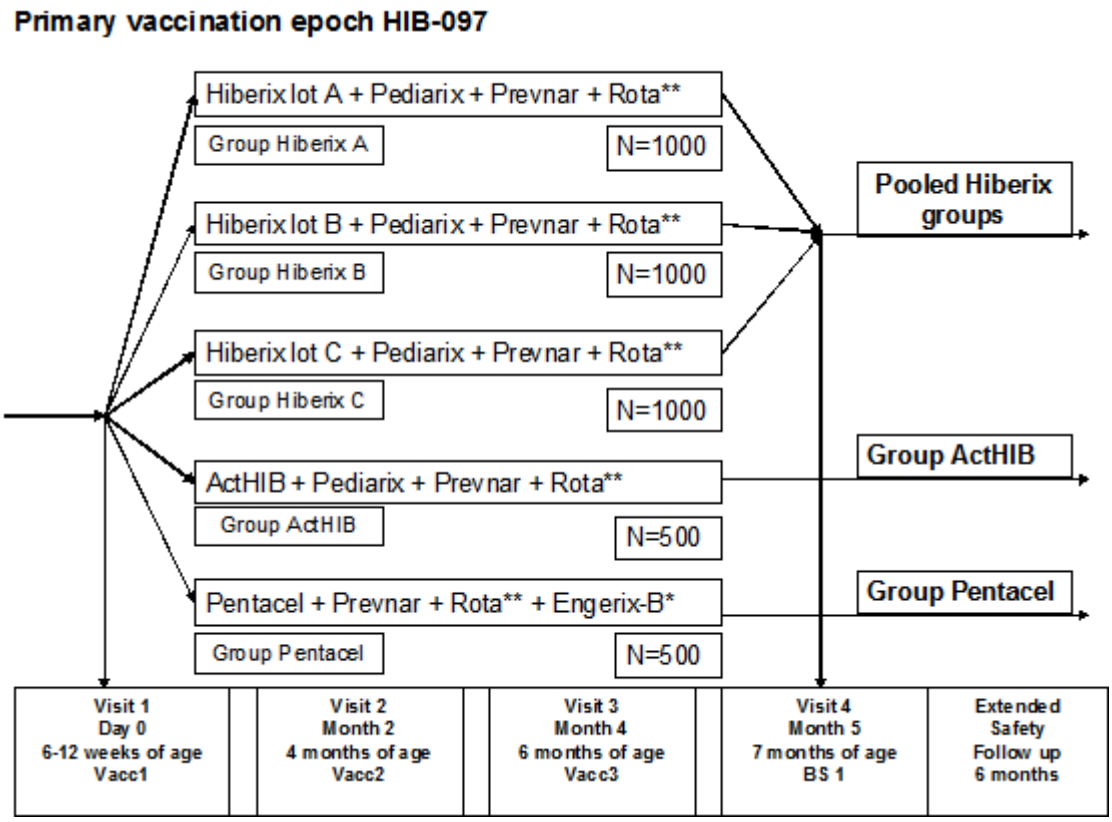
Per the sponsor, study HIB-0097 (112957), consisted of a "Phase III, randomized study, double-blinded for the immunogenicity and consistency evaluation of 3 GSK Biologicals' Hib vaccine lots and single blinded and controlled for the evaluation of safety and immunogenicity of GSK Biologicals' Hib vaccine compared to a monovalent Hib vaccine and open for comparison with a combined DTaP-IPV-Hib vaccine when administered to healthy infants at 2, 4, 6 and 15-18 months of age with recommended co-administrations but at separate sites."

Treatment allocation and blinding for the primary vaccination phase were as follows:

Treatment allocation: randomized with balanced allocation (2:2:2:1:1)

Blinding: The study was double blinded for the 3 *Hiberix* lots and single blinded vs the comparator *ActHIB* and open-label vs the comparator *Pentacel*.

The diagram (from the protocol) below presents a general overview of the primary vaccination epoch**:**



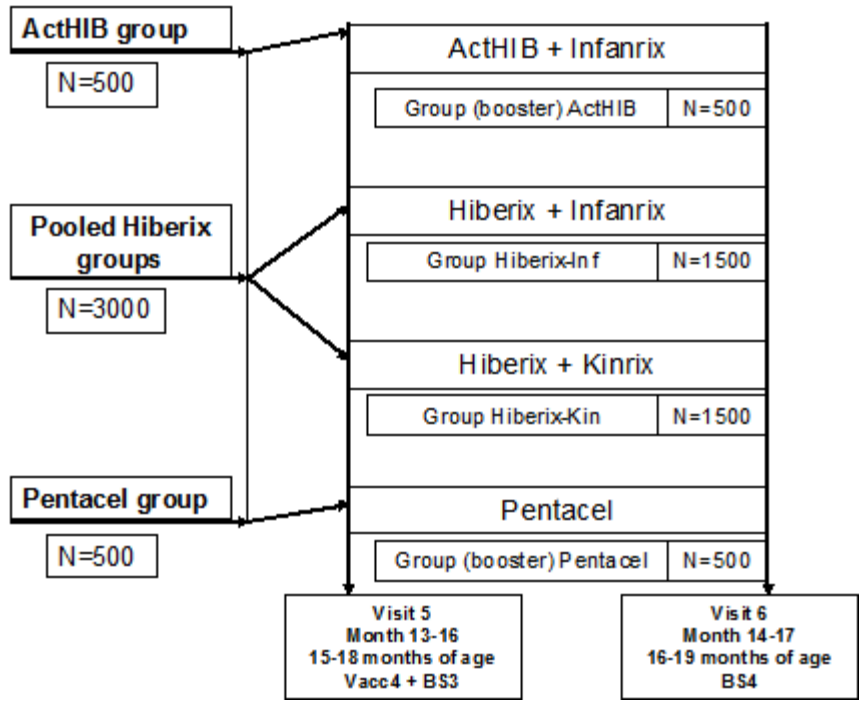
* Engerix-B should not be given at Month 2 (4 months of age) if a birth dose of Hepatitis B vaccine was administered to the subject.
** Rotarix is administered only at Day 0 and Month 2
BS: blood sample; Vacc: vaccination

Treatment allocation and blinding for the booster vaccination phase:

Treatment allocation: The groups primed with *ActHIB* (Group ActHIB) and *Pentacel* (Group Pentacel) during the primary vaccination phase will constitute the Group (booster) ActHIB and Group (booster) Pentacel, respectively, during the booster vaccination phase. The pooled Groups Hiberix A, Hiberix B, and Hiberix C from the primary vaccination phase will be re-randomized with a balanced allocation (1:1) into the Group Hiberix-Inf and Group Hiberix-Kin.
Blinding: The study will be single blinded for the Group Hiberix-Inf, Group Hiberix-Kin and (booster) ActHIB and open-label for the Group (booster) Pentacel.

The sponsor's diagram below presents a general overview of the booster vaccination epoch:

Booster vaccination epoch HIB-097



BS: blood sample; Vacc: vaccination

Number of subjects: For the primary phase, 4000 (1000 subjects in Groups Hiberix A, B and C, 500 subjects in Group ActHIB and Group Pentacel) will be enrolled.

2.3 Statistical Evaluations

Primary endpoints:

Primary vaccination phase (1 month after last dose of primary vaccination):

- Anti-PRP GMCs and anti-PRP concentration ≥1.0 µg/ml
- anti-D antibody concentration ≥0.1 IU/ml
- Anti-T antibody concentration ≥0.1 IU/ml
- Anti-PT GMCs
- Anti-FHA GMCs
- Anti-PRN GMCs
- Anti-Poliovirus 1 antibody titers ≥8 dil^{-1}
- Anti-Poliovirus 2 antibody titers ≥8 dil^{-1}
- Anti-Poliovirus 3 antibody titers ≥8 dil^{-1}
- Anti-4, anti-6B, anti-9V, anti-14, anti-18C, anti-19F and anti-23F GMCs

Booster vaccination phase (+persistence) (1 month after booster vaccination):

- Anti-PRP concentration ≥1.0 µg/ml
- Anti-D antibody concentration ≥0.1 IU/ml Anti-T antibody concentration ≥0.1 IU/ml,

- Anti-PT GMCs,
- Anti-FHA GMCs,
- Anti-PRN GMCs,
- Anti-PT vaccine response rate, defined as the appearance of antibodies in subjects who were seronegative (i.e., concentrations <cut-off value) or at least a two fold increase of pre-vaccination antibody concentrations in subjects who were initially seropositive (i.e., concentrations ≥ cut-off value)
- Anti-FHA vaccine response rate
- Anti-PRN vaccine response rate
- Anti-Poliovirus 1 antibody titers ≥8 dil^{-1},
- Anti-Poliovirus 2 antibody titers ≥8 dil^{-1},
- Anti-Poliovirus 3 antibody titers ≥8 dil^{-1}

Secondary Endpoints:

The secondary endpoints in study HIB-0097 (112957) consists of the following immunogenicity and safety analyses:

Immunogenicity

Primary vaccination phase (1 month after last dose of primary vaccination): anti-PRP GMCs, anti-PRP concentrations ≥0.15 µg/ml and ≥1.0 µg/ml, anti-D concentrations and concentrations ≥0.1 IU/ml (seroprotection), anti-T concentrations and concentrations ≥0.1 IU/ml (seroprotection), anti-PT, anti-FHA and anti-PRN concentrations and concentrations ≥5 EL.U/ml (seropositivity), anti-poliovirus types 1, 2, and 3 antibody titers and titers≥8 dil^{-1} (seroprotection), anti-HBs concentrations and concentrations ≥10.0mIU/ml (seroprotection) and concentrations ≥3.3 mIU/ml (seropositivity), anti-rotavirus antibody concentrations and concentrations ≥20 U/ml, *S. pneumoniae* GMCs, antibody concentrations ≥0.05µg/ml (seropositivity), ≥0.2 µg/mL and ≥0.5 µg/ml for the 7 serotypes in *Prevnar*.

Booster vaccination phase (+persistence):
Prior to the booster vaccination: Anti-HBs concentrations and concentrations ≥10.0mIU/ml (seroprotection) and concentrations ≥3.3 mIU/ml (seropositivity)
Prior to and 1 month after booster vaccination: anti-Poliovirus 1 antibody titers and titers ≥8 dil^{-1} anti-Poliovirus 2 antibody titers and titers ≥8 dil^{-1}, anti-Poliovirus 3 antibody titers and titers ≥8 dil^{-1}, anti-PRP concentration and concentrations ≥0.15 µg/ml, ≥1.0 µg/ml and anti-PRP GMCs

One month after the booster vaccination: anti-D antibody concentration and concentrations ≥0.1 IU/ml, anti-T antibody concentration and concentrations ≥0.1 IU/ml, anti-PT GMCs and concentrations ≥5 EL.U/ml (seropositivity), anti-FHA GMCs and concentrations≥5 EL.U/ml (seropositivity), anti-PRN GMCs and concentrations ≥5 EL.U/ml (seropositivity)

Safety
Primary vaccination phase (1 month after last dose of primary vaccination):

Incidence and intensity of solicited local symptoms (pain, redness, and swelling at the injection site) within 4 days (day 0 to day 3) following each vaccine dose; incidence and intensity of solicited general symptoms (fever, irritability/fussiness, drowsiness, loss of appetite) within 4 days (day 0 to day 3) following each vaccine dose; occurrence of unsolicited symptoms within 31 days following each vaccination; occurrence of all serious adverse events (SAEs) from day 0 until 6 months following the last primary dose or until receipt of the booster vaccination, whichever comes first; occurrence of specific adverse events, i.e., new onset chronic diseases (e.g. autoimmune disorders, asthma, type I diabetes and allergies) and conditions prompting ER visits, from day 0 until 6 months following the last primary dose or until receipt of the booster vaccination, whichever comes first; occurrence of serious adverse events (SAEs) related to study participation, GSK concomitant products and/or leading to death during the entire study.

Booster vaccination phase (+persistence):
Incidence and intensity of solicited local symptoms within 4 days (day 0 to day 3) following the booster dose; incidence and intensity of solicited general symptoms within 4 days (day 0 to day 3) following the booster dose; occurrence of unsolicited symptoms within 31 days following the booster dose; occurrence of all serious adverse events (SAEs) from visit 5 until 6 months following receipt of the booster dose; occurrence of specific adverse events, i.e., new onset chronic diseases (e.g. autoimmune disorders, asthma, type I diabetes and allergies) and conditions prompting ER visits, from visit 5 until 6 months following receipt of the booster dose; occurrence of serious adverse events (SAEs) related to study participation, GSK concomitant products and/or leading to death during the entire study.

2.3.1. Sample size estimation

For power calculation, it is assumed that the number of evaluable subjects will be 80% of tested subjects for immunogenicity evaluation in the primary vaccination phase, with an estimated drop out rate of 20% for the booster vaccination phase.

The power estimation is based on the primary objective of lot-to-lot consistency and the enrollment plan in active phase as follows:

Endpoint	N evaluable Hiberix -PRP per lot	Standard deviation [Log10 concentrations] **	Power*
Anti-PRP GMC(ug/ml)	200	0.68	99.45%
		Total Power =>	98.35%

*[redacted]2-sided equivalence test on mean, alpha=0.05, margin=$\log_{10}(2)$, beta multiplied by 3 to adjust for the 3 pair wise lot comparisons
** Ref: Hib-MenCY-TT005 ActHIB group

If the lot-to-lot consistency of 3 manufacturing lots of *Hiberix* is demonstrated, the above stated co-primary objectives will be evaluated between the pooled *Hiberix* group and other groups, followed by the co-primary objectives in the booster phase.

The sponsor presented the power estimation based on the co-primary objectives in both the primary phase and booster phase (sponsor provided protocol pages 44-47).

2.3.2. Hypothesis

Null hypothesis: $GMC_{Li}/ GMC_{Lj} > 2$ or $GMC_{Li}/ GMC_{Lj} < 0.5$ vs

Alternative hypothesis: $0.5 \leq GMC_{Li}/ GMC_{Lj} \leq 2$, 1 month after 3 primary doses.

Where GMC_{Li}, GMC_{Lj} =geometric mean concentration of anti-PRP in Lot Li, Lj (i, j= A, B, C).

If the null hypothesis is rejected, hypotheses for all the stated co-primary objectives will be evaluated. The sponsor listed all the hypotheses to be tested for the co-primary objectives (please see pages 47-49 of protocol).

2.4 Reviewer's Comments

Comments to CBER review team:

1. For lot-to-lot consistency, CBER recommends that the applicant show that the 95% CI of the GMC ratio is contained within [0.67, 1.5] and the 95% CI of the rate difference is contained within [-10%, 10%]. While using the recommended interval for the rate difference, the sponsor used [0.5, 2.0] for GMC ratio. (GSK has agreed to comply with CBER's recommendation in a response sent on 05/18/2009 and will amend the protocol to reflect the change).
2. Sample size calculations are based on a high estimated drop out rate (20%). The sponsor did not provide any rationale for anticipating a high rate of drop out. I would like the clinical or other reviewer's comment on a possible safety concern on this high rate of drop out. The protocol also doesn't specify how missing data will be handled.
3. The power calculation for the first co-primary objective in the primary vaccine phase is not correct (second table page 44 of the concept protocol).

Pooled Sub-cohorts Hiberix A-PRP, Hiberix B-PRP, Hiberix C-PRP vs Sub-cohort ActHIB-PRP

Endpoint	N evaluable Pooled Sub-cohorts Hiberix A-PRP, Hiberix B-PRP, Hiberix C-PRP	N evaluable Sub-cohort ActHIB-PRP	True rate in both groups**	Power*
Anti-PRP ≥1.0 µg/ml	600	200	85.8%	96.33%

[redacted] Non-inferiority test on two independent proportions, 1-sided, alpha=0.025, margin=10%, power under the alternative hypothesis of equal rates between groups

** Ref: Hib-MenCY-TT005 ActHIB group: 85.8% [80.3; 90.2]

Based on the information provided and using the software indicated (-b(4)- software) the power for sample sizes of 600 from the pooled sub-cohorts Hiberix group and 200 from sub-cohort ActHib is 89.9%, not 96.3% as stated in the protocol.

4. In section 11.2.2 the sponsor lists hypotheses to be tested within the study, but all the hypotheses, except the hypothesis given in d, are not correctly stated to reflect the objectives the sponsor plans to achieve. The statements on the null and alternative hypothesis should be reversed in order to obtain the stated planned objectives.
5. The protocol does not specify the subject recruitment method. Section 2 on page 21 of the concept protocol is titled "Study population and recruitment method plan/period," but no

specific plan is provided on how subjects in each center are to be selected (recruited). One of the problems in the studies that have been conducted early and submitted to support this application is the lack of representativeness of the subjects; for example, most of these studies have disproportionate numbers of subjects by race. Consider, for example, the demographics of study DTPa-HBV-IPV-035 given in the following table.

Characteristics	Categories	Group 3 N = 150 n	%
Race	Black	1	0.67
	White	144	96.00
	Oriental	4	2.67
	Other	1	0.67
Gender	F	78	52.00
	M	72	48.00

Group 3: boosted with DTPa-HBV-IPV + Hib (formulation A)
N = number of subjects
n = number of subjects by category
% = proportion of subjects in a given category

Ninety-six percent of the subjects in the study are from one race category. The recruitment plan/method should be provided in order to determine the appropriateness of the selected subjects to represent the intended target population.

Comments/questions to applicant:

1. Please provide your rationale for not using the CBER recommended [0.67, 1.5] 95% CI of the GMC ratio to show lot-to-lot consistency.
2. On page 51 of the protocol, you stated: "for all antigens and for all analyses (inferential and exploration evaluation of differences between groups), the GMC ratio and its 95% CI will be computed using an ANOVA model." Please specify the ANOVA model you plan to use, showing the specific required assumptions for the selected models that need to be satisfied.
3. The power calculation for the first co-primary objective in the primary vaccine phase is not correct (second table page 44 of the concept protocol).

Pooled Sub-cohorts Hiberix A-PRP, Hiberix B-PRP, Hiberix C-PRP vs Sub-cohort ActHIB-PRP

Endpoint	N evaluable Pooled Sub-cohorts Hiberix A-PRP, Hiberix B-PRP, Hiberix C-PRP	N evaluable Sub-cohort ActHIB-PRP	True rate in both groups**	Power*
Anti-PRP ≥1.0 µg/ml	600	200	85.8%	96.33%

* [redacted] Non-inferiority test on two independent proportions, 1-sided, alpha=0.025, margin=10%, power under the alternative hypothesis of equal rates between groups
** Ref: Hib-MenCY-TT005 ActHIB group: 85.8% [80.3; 90.2]

Based on the information provided and using the software indicated (-b(4)- software), CBER determined that the power for sample sizes of 600 from the pooled sub-cohorts in the Hiberix

group and 200 from sub-cohort ActHib is 89.9%, not 96.3% as stated in the protocol. Please acknowledge.

4. All the hypotheses listed on pages 47-49 to be evaluated after the rejection of the null hypothesis of lot-to-lot consistency, except those in part d, are incorrectly stated. The statements of the null and alternative hypotheses are reversed and will not achieve the intended study objectives. Please acknowledge.
5. On page 21 of the protocol, you stated that currently about 100 centers in the US are anticipated to participate in the study. Please explain how subjects at each of these centers will be selected. Specifically, will subjects be selected proportionally based on certain characteristics (gender, race, etc.) to be representative of the target population for intended use? Please also provide the planned (anticipated) number of subjects in each center.

6. Part i of the list of the hypotheses reads

   i) Null hypothesis: $GMC_{Hiberix+Kinrix(booster)} - GMC_{Hiberix + Infanrix(booster)} < 0.67$

   Alternative hypothesis: $GMC_{Hiberix+Kinrixx(booster)} - GMC_{Hiberix + Infanrix(booster)} \geq 0.67$

GMC ratios should be used instead of differences. Please acknowledge.

3. Study DTPa-IPV- 026

The review in this section covers the modified study report 213503/026 (DTPa-IPV-026). The original clinical study dated April 12, 1999 was conducted in Lithuania. The study was conducted outside of FDA IND regulation, and no part of the study was reviewed or concurred upon by CBER/FDA.

Study DTPa-IPV- 026 was an open label, randomized clinical study to assess the reactogenicity and immunogenicity of SB Biologicals' DTPa vaccine co-administered with SB Biologicals' Hib vaccine in two concomitant injections into opposite limbs, as compared to SB Biologicals' DTPa vaccine mixed with SB Biologicals' Hib vaccine and to SB Biologicals' DTPa-IPV vaccine mixed with SB Biologicals' Hib vaccine, administered as a booster dose to healthy children in their second year of life, previously primed with three doses of SB Biologicals' DTPa-HBV-IPV vaccine.

Analyses and data presented in the modified study report are limited to the group receiving DTPa co-administered with Hiberix at separate injection sites (study group 1).

3.1 Study Objectives:

Primary:

To evaluate and compare the local reactogenicity of the three booster vaccination regimens.

Secondary:

To evaluate the general (systemic) reactogenicity of the vaccines used in all groups

- To assess the immunogenicity of the vaccines administered, in terms of the antibody response to diphtheria and tetanus toxoids, the three pertussis antigens PT, FHA, and PRN, poliovirus types 1, 2, and 3 and PRP
- To evaluate in all groups the persistence of antibodies induced by the combined DTPa-HBV-IPV vaccine used in the primary vaccination course.

3.2 Study Design

Study DTPa-IPV- 026 was an open-label, randomized clinical study with healthy children, aged 15 to 21 months (protocol-specified age: 15 to 24 months) who had completed the three-dose primary vaccination course of DTPa-HBV-IPV and Hib (SB Biologicals or Pasteur-Mérieux-Connaught [PMC]) vaccines during study DTPa-HBV-IPV-012, enrolled in three groups: Group 1 (DTPa + Hib + OPV), Group 2 (DTPa/Hib + OPV), Group 3 (DTPa-IPV/Hib.

Analyses and data presented in this report are limited to group 1, the group receiving DTPa co-administered with Hiberix at separate injection sites (DTPa + Hib + OPV).

3.3 Statistical Evaluation

Two hundred and seventy-three healthy male and female children, previously primed in the study DTPa-HBV-IPV-012, were enrolled to receive a booster vaccination at the age of 15 to 24 months. The allocation of subjects in group 1 is:

Primary Phase (DTPa-HBV-IPV-012)	Booster Phase (DTPa-IPV-026) Group 1 DTPa + Hib + OPV (N= 92) n
DTPa-HBV-IPV + Hib (PRP-T, SB) (N = 219)	64
DTPa-HBV-IPV + Hib (PRP-T, PMC) (N = 110)	28

N= number of subjects enrolled
n= number of subjects enrolled in the booster study according to primary groups

Number of subjects: overall enrolled = 273, completed study=271.
Total cohort in group 1 = 92

According to Protocol (ATP) reactogenicity (primary analysis) in group 1= 65
ATP immunogenicity cohort (primary analysis) in group 1= 60

3.3.1 Analysis of immunogenicity

Analysis of immunogenicity was performed for the ATP cohort for immunogenicity (all evaluable subjects (i.e., those meeting all inclusion/exclusion criteria and complying with the

procedures defined in the protocol) for whom assay results were available for antibodies against at least one study vaccine antigen component) and for the total cohort.

Pre-booster serological status

The pre-booster serological status of subjects included in the immunogenicity analysis with respect to antibodies against each vaccine antigen is presented in the following table (table 9 in the applicant's report)

Pre-booster serological status of subjects with respect to antibodies to each vaccine antigen; subjects included in the ATP analysis of immunogenicity

Antibody	Status	Group 1	
		n	%
Anti-diphtheria	S+	39	65.0
	S-	21	35.0
Anti-tetanus	S+	57	95.0
	S-	3	5.0
Anti-PT	S+	52	86.7
	S-	8	13.3
Anti-FHA	S+	57	100.0
	S-	0	0.0
Anti-PRN	S+	57	95.0
	S-	3	5.0
Anti-PRP	S+	56	93.3
	S-	4	6.7
Anti-polio 1	S+	54	96.4
	S-	2	3.6
Anti-polio 2	S+	56	100.0
	S-	0	0.0
Anti-polio 3	S+	54	96.4
	S-	2	3.6

Group 1: DTPa + Hib and OPV
S- = pre-vaccination seronegative for the corresponding antibody
S+ = pre-vaccination seropositive for the corresponding antibody
n = number of subjects of a specified serological status

Approximately one year after the primary vaccination course, at least 86.7% of subjects in group 1 were seropositive for anti-tetanus, anti-PT, anti-FHA, anti-PRN, anti-PRP, and anti-polio types 1, 2, and 3 antibodies, indicating persistence.

Anti-diphtheria and anti-tetanus antibody response

Seropositivity rates (%) and GMTs of anti-diphtheria and anti-tetanus antibodies for the subjects included in the ATP analysis immunogenicity are presented in table 1 and table 2, respectively (tables 11 and 12 of applicant's report).

Table 1: Seropositivity rates (%) and GMT's of anti-diphtheria antibodies; subjects included in the ATP analysis of immunogenicity

Group	Timing	N	S+		95%CI		GMT	95%CI	
			n	%	L.L.	U.L.	(IU/ml)	L.L.	U.L.
1	Pre	60	39	65.0	52.1	77.9	0.146	0.114	0.185
	Post	60	60	100.0	92.5	100.0	5.415	4.296	6.825

Group 1: DTPa + Hib and OPV
Pre = pre-booster, Post = approximately one month after the booster dose,
S+ = titres ≥0.1 IU/ml
N = total number of subjects tested, n = number of subjects with titres ≥ 0.1 IU/ml
95% CI, L.L. and U.L. = 95% Confidence Interval, Lower and Upper limits

One month after the booster dose, all subjects had anti-diphtheria antibody titers ≥0.1 IU/ml. An increase in GMT's of 37-fold for group 1, was observed one month after the booster dose as compared to the pre-booster titers.

Table 2: Seropositivity rates (%) and GMT's of anti-tetanus antibodies; subjects included in the ATP analysis of immunogenicity

Group	Timing	N	S+		95%CI		GMT	95%CI	
			n	%	L.L.	U.L.	(IU/ml)	L.L.	U.L.
1	Pre	60	57	95.0	85.2	98.7	0.397	0.321	0.491
	Post	60	60	100.0	92.5	100.0	10.872	8.802	13.429

Group 1: DTPa + Hib and OPV
Pre = pre-booster, Post = approximately one month after the booster dose,
S+ = titres ≥0.1 IU/ml
N = total number of subjects tested, n = number of subjects with titres ≥ 0.1 IU/ml
95% CI, L.L. and U.L. = 95% Confidence Interval, Lower and Upper limits

All subjects had anti-tetanus antibody titers ≥ 0.1 IU/ml one month after the booster dose. There was an increase of approximately 27-fold in the GMT's of groups 1, one month after the booster dose as compared to the pre-booster titers.

Reviewer's comment: *The immunogenicity metric, seropositivity rate one month after the booster dose, is not statistically different compared to the pre-booster rate. (See comment # 3 in section 6.4.)*

Anti-pertussis antibody response

The vaccine response rates for each pertussis antigen for subjects included in the ATP analysis of immunogenicity, categorized according to pre-booster vaccination status, is presented in table 3 (Table 13 in applicant's report) and the seropositivity rates (%) and GMT's of each pertussis antigen for subjects included in the ATP analysis of immunogenicity is presented in table 4 (table 14 in applicant's report).

Table 3: Booster vaccine response: Pertussis antigens; subjects included in the ATP analysis of immunogenicity

Antibody	Group	Pre-vaccination status	N	n	Vaccine Response % [95% CI]
Anti-PT	1	S-	8	8	100.0
		S+	52	51	98.1
		Total	60	59	98.3
					[89.9 , 99.9]
Anti-FHA	1	S+	57	54	95.0
		Total	57	54	95.0
					[84.5 , 98.6]
Anti-PRN	1	S-	3	3	100.0
		S+	57	54	94.7
		Total	60	57	95.0
					[85.2 , 98.7]

Group 1: DTPa + Hib and OPV
N = total number of subjects tested
n = number of subjects with a vaccine response
95% CI = 95% Confidence Interval
S+ = titres ≥5 EL.U/ml , S- = titres <5 EL.U/ml
Vaccine response definition:
For pre-booster seronegative subjects (S-): Appearance of titre (≥ 5 EL.U/ml)
For pre-booster seropositive subjects (S+): At least two-fold increase in pre-vaccination titre

All subjects initially seronegative to anti-PT, anti-FHA, and anti-PRN antibodies showed a vaccine response.

Table 4: Seropositivity rates (%) and GMT's of anti-PT, anti-FHA and anti-PRN antibody titers; subjects included in the ATP analysis of immunogenicity

Antibody	Gp	Timing	N	S+		95%CI		GMT	95%CI	
				n	%	L.L.	U.L.	(EL.U/ml)	L.L.	U.L.
Anti-PT	1	Pre	60	52	86.7	74.9	93.7	10.8	8.7	13.4
		Post	60	60	100.0	92.5	100.0	127.3	108.4	149.6
Anti-FHA	1	Pre	57	57	100.0	92.1	100.0	40.1	30.0	53.5
		Post	60	60	100.0	92.5	100.0	597.4	483.4	738.2
Anti-PRN	1	Pre	60	57	95.0	85.2	98.7	26.7	20.5	34.9
		Post	60	60	100.0	92.5	100.0	814.9	634.5	1046.6

Gp = group
Group 1: DTPa + Hib and OPV
Pre = pre-booster vaccination, Post = approximately one month after the booster dose
S+ = titres ≥5 EL.U/ml
N = total number of subjects tested, n = number of subjects with titres ≥ 5 EL.U/ml
95% CI, L.L. and U.L. = 95% Confidence Interval, Lower and Upper limits

All subjects had anti-PT, anti-FHA, and anti-PRN antibody titres ≥ 5 EL.U/ml one month after the booster dose. There was an increase of 12-fold in the GMT's for anti-PT, 15-fold for anti-FHA, and 31-fold for anti-PRN antibodies in group 1.

Reviewer's comment: *There is no statistical significance between number of subjects who had anti-FHA and anti-PRN antibody titres* ≥ 5 EL.U/ml pre and post booster dose (*See comment # 3 in section 6.4.)*

Anti-polio antibody response
The seropositivity rates (%) and GMTs for each polio antigen for subjects included in the ATP analysis of immunogenicity is presented in table 5 (table 15 in applicant's report).

Table 5: Seropositivity rates (%) and GMTs of anti-polio antibody titres; subjects included in the ATP analysis of immunogenicity

Antibody	Gp	Timing	N	S+		95%CI		GMT	95%CI	
				n	%	L.L.	U.L.		L.L.	U.L.
Anti-polio 1	1	Pre	56	54	96.4	86.6	99.4	67.5	50.3	90.5
		Post	56	56	100.0	92.0	100.0	1658.0	1183.4	2323.0
Anti-polio 2	1	Pre	56	56	100.0	92.0	100.0	76.4	59.5	98.0
		Post	56	56	100.0	92.0	100.0	5681.2	4579.2	7048.3
Anti-polio 3	1	Pre	56	54	96.4	86.6	99.4	113.0	81.7	156.2
		Post	55	55	100.0	91.9	100.0	2471.9	1668.6	3662.1

Group 1: DTPa + Hib and OPV
S+= titres ≥ 8
n = number of subjects with titres ≥8

All subjects had anti-polio 1 and 2 antibody titers ≥ 8 one month after the booster dose. A 22-25 fold increase was observed in group 1 for anti-polio1 and anti-polio 3 antibody titers, and a 74-fold increase for anti-polio 2 antibody titers.

Reviewer's comment: *The immunogenicity metric, seropositivity rate, is not statistically significant.* The seropositivity rates of anti-polio antibody titers before and after the booster dose *are not statistically different. (See comment # 3 in section 6.4.)*

Anti-PRP antibody response

Table 6 (table 16 in applicant's report) presents percentages of subjects with anti-PRP titers ≥ 0.15 mcg/ml and ≥ 1.0 mcg/ml, as well as the GMT's for the subjects included in the ATP analysis of immunogenicity.

Table 6: GMT's and distribution of anti-PRP antibodies; subjects included in the ATP analysis of immunogenicity

Gp	Timing	N	≥0.15 mcg/ml		95% CI		≥1.0 mcg/ml		95% CI		GMT	95% CI	
			n*	%	L.L.	U.L.	n**	%	L.L.	U.L.	(mcg/ml)	L.L.	U.L.
1	Pre	60	56	93.3	83.0	97.8	19	31.7	19.1	44.3	0.731	0.524	1.021
	Post	60	60	100.0	92.5	100.0	60	100.0	92.5	100.0	80.022	59.382	107.83

Group 1: DTPa + Hib and OPV
Gp = group
Pre = pre-booster vaccination, Post = approximately one month after the booster dose
N = total number of subjects tested
n* = total number of subjects with titres ≥0.15 mcg/ml
n** = total number of subjects with titres ≥1.0 mcg/ml
95% CI, L.L. and U.L. = 95% Confidence Interval, Lower and Upper limits

All subjects were seropositive (titres ≥ 0.15 mcg/ml) to anti-PRP antibodies and had titres ≥ 1.0mcg/ml in group 1 one month after the booster vaccination. There was an increase of 109-fold in the GMT for group 1.

Reviewer's comment: The reviewer conducted immunogenicity analysis for the total cohort (ITT) for immunogenicity (all subjects for whom data concerning immunogenicity were available) based on data provided by the sponsor. The results are consistent with those of the ATP analysis provided by the applicant.

Safety and Reactogenicity

For the sixty-five subjects included in the ATP analysis of reactogenicity, all diary cards were returned to the investigator, resulting in compliance of 100%. The percentage of subjects with at least one local adverse experience (solicited or unsolicited), with at least one general adverse experience (solicited or unsolicited), and with at least one adverse experience (solicited or unsolicited) during the 4-day follow-up period is presented in table 7 (Table 5 (page 27) in the applicant's report).

Table 7: Incidence and nature of symptoms (solicited and unsolicited) after the booster dose during the four-day follow-up period; subjects included in the ATP analysis of reactogenicity.

		Any symptom		General symptoms		Local symptoms		Per separate site			
								DTPa		Hib	
Gp	N	n	%	n	%	n	%	n	%	n	%
1	65	52	80.0	29	44.6	45	69.2	38	58.5	30	46.2

Gp = Group; Group 1: DTPa + Hib and OPV
N = total number of doses administered with a symptom sheet returned (i.e. documented doses)
Includes both solicited and unsolicited symptoms reported
n = total number of documented doses followed by the specified symptoms

All solicited local reactions were considered causally related to vaccination. Redness at the injection site was the most frequently reported local symptom (63.1%). There were no cases of pain preventing normal daily activities. "Sleeping less than usual" was the most frequently reported general solicited symptom (30.8%). The majority of all reported solicited general symptoms had an onset within the first 48 hours after vaccination.

A total of 11 unsolicited signs and symptoms were reported. All the unsolicited symptoms were general symptoms and 'not related' to vaccination as determined by the investigator. None of these symptoms were of grade 3 intensity.

GSK's over all conclusion

No vaccine related SAEs or unsolicited symptoms were reported.

The DTPa, Hib, and OPV vaccines were immunogenic when administered as a booster dose. One month after the booster dose, all subjects were seropositive for anti-diphtheria, anti-tetanus, anti-PT, anti-FHA, anti-PRN, anti-PRP, and anti-polio 1, 2, and 3 antibodies. All subjects had anti-PRP antibody concentrations ≥ 1.0 mcg/ml.

Hence, these data suggest that all the study vaccines were immunogenic and safe when administered as a booster dose at the age of 15 to 24 months.

3.4 Reviewer's comments

1. The study was conducted outside of the US and was not under FDA/CBER IND regulation. Hence, CBER did not review or concur with the proposed protocol and the study report during and after the clinical trial or study.

2. The analyses and all data presented in this BLA are for subjects 15 to 19 months of age, the group who received DTPa co-administered with Hiberix at separate injection sites (study group 1). Demographic data for the subjects included in the ATP analysis of reactogenicity and immunogenicity are below:

   Subjects included in the ATP analysis of immunogenicity

Sex	N	Mean age (months)	S.D	Min age (months)	Max age (months)
Male	36	17.1	1.05	15	19
Female	24	17.5	1.22	15	19
Total	60	17.3	1.13	15	19

   Subjects included in the ATP analysis of reactogenicity

Sex	N	Mean age (months)	S.D	Min age (months)	Max age (months)
Male	38	17.1	1.04	15	19
Female	27	17.3	1.33	15	19
Total	65	17.2	1.17	15	19

   However,the age group specified in the protocol and the conclusion (inference) drawn by the applicant is for subjects 15 to 24 months of age.

3. The protocol of the study, which was not reviewed under FDA IND regulation, lacks a planned statistical method for both immunogenicity and reactogenicity analysis. It fails to specify the criteria to evaluate vaccine response. Moreover, it is not clear whether the specified secondary endpoints are (or need) to be used as co-primary endpoints.

I would also like to point out the following:

The secondary endpoints as per the protocol are: antibodies to the three pertussis antigens PT, FHA and PRN: percentage of vaccine response and percentage of subjects eliciting titers ≥ 5 EL.U/ml and GMTs before and one month after the booster dose. For antibodies to the Hib polysaccharide PRP: percentages of subjects eliciting titres ≥ 0.15 µg/ml, ≥ 0.5 µg/ml, and ≥ 1.0 µg/ml, and GMTs before and one month after the booster dose. For antibodies to diphtheria and tetanus toxoid: percentage of subjects eliciting titres ≥ 0.1 IU/ml and GMTs before and one month after the booster dose.

However, in the results of the analysis of immunogenicity (tables 9 to 14 above):

- There is no statistically significant difference in percentage of subjects eliciting titers ≥ 5 EL.U/ml before and after the booster dose for anti-FHA and anti-PRN antibody titers (table 4 above or table 14 in the applicant's report). The applicant concludes that all subjects had anti-FHA and anti-PRN antibody titers ≥ 5 EL.U/ml one month after the booster dose, but all subjects had already anti-FHA titer ≥ 5 EL.U/ml and 95% of subjects had anti-PRN titer of ≥ 5 EL.U/ml before the booster dose.
- There is no statistical significance between the percentage of subjects who elicited anti-tetanus antibody titers ≥ 0.1 IU/ml before and after the booster dose. (Ref: Table 2 above or table 12 in applicant's report).
- There is no statistical significance between the seropositivity rates of anti-polio antibody titers before and after the booster dose. (Ref: Table 5 above or table 15 in applicant's report).
- There is no statistical significance between the seropositivity rates (titers ≥ 0.15µg/ml) of anti-PRP antibodies before and after the booster dose. (Ref: Table 6 above or table 16 in applicant's report).

-

In light of these notes, even though seropositivity is considered as an immunogenicity endpoint, the applicant's conclusion regarding immunogenicity is only based on the evaluation of the GMTs. It should also be noted that assessment of seroresponse (seropositivity) data provides per-subject information that may not be captured using only GMTs.

4. The reviewer was able to verify the results of the immunogenicity and safety analyses performed by the sponsor. Although I obtained a slightly different 95% CI for the seropositivity rate of anti-polio 1 titers ([84.2-95.6] for pre-vaccination and [90.8-100] for post vaccination), the differences do not alter the overall conclusion.

5. To ensure the deviations from the protocol were not treatment related and did not lead to bias in the result, I analyzed the total cohort (ITT) for immunogenicity (all subjects for whom data concerning immunogenicity were available). The immunogenicity results are consistent with those of the ATP analysis provided in the report by the applicant.

4. Study DTPa-HBV- 032

This study report is a modified report of the original clinical study report for study DTPa-HBV-032 dated August, 2000. Immunogenicity analyses and data presented in this modified study report are limited only to the response to PRP at the booster phase.

The study was a multi-center, open-label clinical study of the immunogenicity and reactogenicity of SmithKline Beecham (SB) biologicals' DTPa-HBV vaccine, when co-administered with SB Biologicals' Hib vaccine in two concomitant injections into opposite limbs, as a primary vaccination course in healthy infants aged 2, 4, and 6 months, followed by a booster dose administered according to the local expanded program on immunization schedule.

4.1 Objectives

Primary objective:
The primary objective of study DTPa-HBV-032 was to assess the antibody response to the Hib capsular polysaccharide polyribosyl-ribitolphosphate (PRP) antigen and the recombinant hepatitis B surface antigen (HBsAg) after the third dose and after the booster dose.

Secondary objective:

- To assess the antibody response to the pertussis toxin and diphtheria and tetanus toxoids after the third vaccine dose in a subset of approximately 120 vaccinees (30 per study centre).
- To assess persistence of the aforementioned antibodies until the time of the booster vaccination.
- To assess the incidence, nature and relationship of adverse events after each dose.

4.2 Study Design

The study was designed as an open-label, single group, multi-country (Argentina and Brazil) and multicenter study of a 3 dose primary vaccination course at 2, 4, and 6 months of age with booster administration at the age recommended in local pediatric immunization programme(s). The study comprised a 4-visit primary vaccination phase: Visit 1 (study month 0), visit 2 (M2), visit 3 (M4), and visit 4 (M5; PIII); and a 2-visit Booster Phase: Visit 5 (M14-16; Pre-Booster) and Visit 6 (M15-17; Post-booster).

4.3 Statistical evaluations

The study report presents only endpoints and analyses for PRP for the booster phase in terms of immunogenicity analysis.

Primary endpoint:

- Anti-PRP antibody titres ≥ 0.15 mcg/ml

Secondary endpoint:

- Anti-PRP antibody titres ≥ 1.0 mcg/ml;
- Occurrence of solicited symptoms during the 4-day follow-up period after each vaccine dose;
- Occurrence of unsolicited symptoms occurring within 30 days after each vaccine dose;
- Occurrence of Serious Adverse Events during the entire study period

Reviewer's comment: *It's not clear whether GMT or percentage of subjects with anti-PRP antibody titres ≥ 0.15 mcg/ml is the primary/secondary endpoint. As per protocol, the primary and secondary endpoints were:*
Primary: - percentage of infants with titers of antibodies to PRP ≥ 0.15 μg / ml
- percentage of infants with titers of antibodies to HBs antigen ≥ 10 mIU/ml.

4.3.1 Analysis of Immunogenicity

Both Total and ATP cohort analyses of immunogenicity data were performed. The ATP analysis was specified as the analysis of primary interest.

Seropositivity/Seroprotection rates and geometric mean titre (GMT) with 95% confidence intervals were calculated for anti-PRP antibodies at the pre-and post-booster blood sampling time points and are presented in Table 8 and Table 9, respectively, for subjects in the total cohort. Seropositivity was defined as antibody titre ≥ assay cut-off: anti-PRP (0.15 mcg/ml). In addition, percentages with anti-PRP titres ≥1.0 mcg/ml with 95% CI were calculated. Steep

Table 8: Anti-PRP titres ≥0.15 mcg/ml and ≥1.0 mcg/ml in subjects in the total cohort

Timing	N	≥0.15 mcg/ml			≥1.0 mcg/ml		
			95% CI			95% CI	
		%	LL	UL	%	LL	UL
Pre-booster	147	97.3	93.2	99.3	66.7	58.4	74.2
Post-booster	141	100.0	97.4	100.0	100.0	97.4	100.0

Table 9: Anti-PRP GMTs for subjects in the total cohort.

Timing	N	**Geometric mean titres (GMT) (mcg/ml)**			Min	Max
			95% CI			
		value	LL	UL		
Pre-booster	147	2.007	1.579	2.551	<0.15	246.205
Post-booster	141	129.690	104.665	160.698	1.244	1485.360

Results: Seropositivity increased following the booster dose; geometric mean titres (GMTs) followed a similar pattern. Both seropositive and negative subjects responded strongly to the booster dose and showed marked increases in GMT values.

Reviewer's comment: *The proportion of subjects who have anti-PRP titres ≥0.15 mcg/ml pre-booster dose is not statistically significantly different from the proportion post-booster dose (P-value=0.1419).*

4.3.2 Analysis of Safety

Data concerning solicited and unsolicited signs and symptoms reported following 719 doses documented on symptom sheets and returned to the sponsor are reported. All safety findings are reported from the ATP population of reactogenicity (N = 190).

Over the three-dose primary vaccination, the nature of symptoms reported was more general than local after each dose of the three-dose primary vaccination course; however, the reverse was observed following the booster dose.

Table 10 details the incidence of both solicited (local and general) and unsolicited adverse events reported over the 4-day follow-up period (Day 0 to 3) after each vaccine dose. This table includes both solicited and unsolicited symptoms reported on symptom sheets during the 4-day follow-up period. If one symptom was reported more than once after a given dose, it was counted only once.

Table 10: ATP analysis of safety

		Symptoms				**General**				**Local**			
				95% CI				95% CI				95% CI	
	N	n	%	LL	UL	n	%	LL	UL	N	%	LL	UL
Dose 1	189	107	56.6	49.2	63.8	90	47.6	40.3	55	61	32.3	25.7	39.4
Dose 2	186	91	48.5	41.5	56.3	69	37.1	30.1	44.5	52	28	21.6	35
Dose 3	179	73	40.8	33.5	48.4	56	31.3	24.6	38.6	44	24.6	18.5	31.6
Dose 4	140	80	57.1	48.5	65.5	57	40.7	32.5	49.3	64	45.7	37.3	54.3
Total doses	694	351	50.6	46.8	54.4	272	39.2	35.5	42.9	221	31.8	28.4	35.5
Overall Subjects	190*	159*	83.7*	77.6	88.6	142*	74.7*	67.9	80.7	113*	59.5*	52.1	66.5

A single dose is the simultaneous administration of both the DTPa-HBV and the Hib vaccines at any one visit.
Dose 1-3= 3 dose primary vaccination course
Dose 4 = booster dose
N = total number of documented administrations of each dose.
n = number of documented doses with at least one (type of) symptom
% = percentage of documented doses followed by at least one (type of) symptom
*: Overall subjects, the total number of subjects with at least one documented dose
Local: local symptoms reported for any vaccination site

GSK's overall conclusion

1. The Hib vaccine elicited high antibody titres to PRP.
2. Seropositivity was maintained for approximately one year in the majority of subjects prior to the booster dose, which stimulated a higher antibody response.
3. The vaccines administered were safe and well-tolerated.

4.4 <u>Reviewer's Comments and analysis of immunogenicity:</u>

1. The study was conducted outside of the US and was not under FDA/CBER IND regulation. Hence, CBER did not review and concur on the protocol and the study report during and after the trial was conducted in 1998.
2. The protocol lacks a properly formed statistical hypothesis and pre-specified method of analysis to be conducted during the clinical trail.
3. The applicant indicated that the protocol for this study report has been amended to reflect certain changes on June 17th, 1998. Neither the original protocol nor the amendment was reviewed or concurred on by CBER.

4. Immunogenicity analyses and data presented are limited only to the response to PRP at the booster phase. The primary statistic specified in the protocol "the percentage of infants with titers of antibodies to PRP $\geq 0.15\ \mu g/ml$" is not used to access immunogenicity. The applicant reported anti-PRP seropositivity/seroprotection rates (proportion of subjects with titres ≥ 0.15 mcg/ml and the proportion of subjects with titres ≥ 1.0 mcg/ml) with 95% confidence intervals for subjects in the total cohort for pre and post booster vaccination (Table 8 above) and conclude that the booster vaccine elicited high antibody titres to PRP. However, the applicant did not establish statistically significant difference between the pre and post vaccination rates.
5. There was a high rate of dropouts (29%). Even though none of the dropouts appear to be related to adverse event (safety), I am concerned that the high rate of drop out might influence and bias the results and the conclusions reached.
6. I agreed with the applicant's rationale to change the analysis of primary interest for immunogenicity from ATP to total cohort. Originally the principal analysis of immunogenicity was to be of the ATP cohort for immunogenicity, but due to eliminations resulting from protocol violations and noncompliance with the protocol procedure, the number of evaluable subjects was below the planned evaluable population. Therefore, the principal immunogenicity analysis is based on the total cohort. I performed the immunogenicity analysis using both the ATP and TVC cohorts for immunogenicity and was able to verify results obtained by the applicant.

5. Study DTPa-HBV- 020

This study report is a modified report of the study DTPa-HBV-020 dated August 9, 1999. Analyses and data presented are limited to the group receiving DTPa-HBV co-administered with Hiberix at separate injection sites (study group 1) and, with regard to immunogenicity, to the response to PRP only.

The study is an open-label study to assess the immunogenicity and reactogenicity of SB Biologicals' DTPa-HBV and dtpa-HBV vaccines when administered with SB Biologicals' Hib vaccine, either mixed in one syringe and given in one single injection or given in two simultaneous injections into opposite limbs, as a booster vaccination at the age of 15 to 22 months to healthy children, previously primed with a three-dose primary vaccination course using the DTPa-HBV vaccine.

The original study was an open-label, randomized study with four groups. All subjects enrolled in the study had previously participated in study DTPa-HBV-004 or DTPa-HBV-007 (consistency phase) and were to have received a complete primary vaccination course.

5.1 Objectives

Primary:
To assess the immunogenicity of the fourth dose of SB Biologicals' Hib and DTPa-HBV, DTPa-HBV vaccines.

Secondary:

To evaluate and compare the reactogenicity in all subjects after administration of the study vaccines.

The primary objective of the original study DTPa-HBV-020 was:

- To assess the immunogenicity of SB Biologicals' combined DTPa-HBV, DTPa-HBV and Hib vaccines when given as a fourth dose, either in one injection or given separately in the opposite limbs.

The secondary objective was:

- To evaluate the local and general reactogenicity of the study vaccines when given as a fourth dose in all subjects.

5.2 Study Design

The study was an open-label, randomized study with four groups. All subjects enrolled in the study had previously participated in study DTPa-HBV-004 or DTPa-HBV-007 (consistency phase) and were to have received a complete primary vaccination course.

Only analysis on study group 1 was used for this BLA (modified Hiberix BLA only) and this group received a separate dose of DTPa-HBV + Hib (subjects received primary vaccination of DTPa-HBV + Hib in study DTPa-HBV-004).

5.3 Statistical Evaluations

Sample size: 553 total subjects were enrolled in the study, and 138 subjects were enrolled in group 1. Within group 1, the number of :

- Subjects for immunogenicity analysis (ATP) = 108
- Subjects for reactogenicity analysis (ATP) = 129.

5.3.1 Analysis of Immunogenicity

Data from 108 subjects were eligible to be included in the ATP immunogenicity analysis. Seropositivity rates and GMTs of anti-PRP antibodies for subjects included in the ATP analysis of immunogenicity are shown in table 11.

Table 11: Seropositivity rates and GMTs of anti-PRP antibodies

Timing	N	≥ 0.15 mcg/ml				GMT		
				95% CI			95% CI	
		n	%	LL	UL	Mcg/ml	LL	UL
Pre	108	84	77.8	68.6	85.0	0.58	0.43	0.80
PI(d30)	108	108	100.0	95.7	100.0	96.12	74.07	124.73

N = total number of subjects tested; n = subjects with titres ≥0.15 mcg/ml
Pre = pre booster vaccination (day 0); PI(d30) = approximately one month after booster vaccination
For GMT calculations, undetectable titres of antibodies (<0.15 mcg/ml) were given an arbitrary value of 0.075 mcg/ml

All subjects had anti-PRP antibody titers ≥ 0.15 mcg/ml and titers ≥ 1.0 mcg/ml, one month after the booster dose. The anti-PRP GMTs increased from pre- to post-booster 164 fold.

5.3.2 Analysis of safety and reactogenicity

For the 129 subjects included in the reactogenicity analysis, a total of 129 doses of vaccine were administered, and a total of 128 symptom sheets in group 1 were returned.

Overall, symptoms (including local, general, solicited or unsolicited) within the four days after the booster vaccination were reported following 62% of the doses administered.

The incidence and nature (local or general) of solicited and unsolicited symptoms for subjects included in the ATP analysis of reactogenicity are presented in the following table (table 12).

Table 12: Incidence and nature of symptoms after vaccination, within the 4-day follow-up period after vaccination

	Any symptoms		General symptoms					Local symptoms	Combined vaccine site*		Hib vaccine site	
				All		R or PR						
N	n	%	N	n	%	n	%	N	n	%	n	%
129	80	62.0	128	63	49.2	60	46.9	128	44	34.4	37	28.9

*combined vaccine corresponding to the product administered to each group i.e. DTPa-HBV
N = number of documented doses
n = number of documented doses followed by the specified symptom
R or PR = related or possibly related to vaccination

GSK's Conclusion

Substantial increases in anti-PRP antibody titers post-booster vaccination were observed. All subjects, who received a booster dose of SB Biologicals' DTPa-HBV vaccine with SB Biologicals' Hib vaccine administered separately, reached the concentration of 1.0 mcg/ml.

The most frequently reported local symptom was redness and the most frequently reported general symptom was fever.

In summary, GSK concludes that these results indicate that the Hib vaccine administered separately with the DTPa-HBV vaccine was safe and elicited a booster response.

5.4 Reviewer's comment

1. CBER/FDA did not review the original study report and the protocol of the study. (No IND was submitted for this study to CBER/FDA). The protocol suffers many drawbacks:
    - It fails to appropriately define the primary and secondary endpoints
    - It fails to specify criteria to assess the primary and secondary objectives

2. I was able to verify the descriptive statistical analysis results reported. Only descriptive statistical results are relevant to the group (subjects in group 1) considered under this BLA.

3. On the immunogenicity analysis, I obtained slightly different results from the applicant's reported results using the data provided by the applicant. Nevertheless, the differences do not alter the overall conclusion of GSK.

6. Study DTPa-IPV- 013p

This is a modified study report produced for the purpose of the Hiberix US BLA. Analyses and data presented are limited to the group receiving DTPa-IPV co-administered with Hiberix at separate injection sites (study group 2) and, with regard to immunogenicity, to the response to PRP only. The full original clinical study report is dated June 20, 1996.

It was an open-label randomized clinical study to assess the immunogenicity and reactogenicity of co-administration of SmithKline Beecham Biologicals' DTPa-IPV vaccine, and SmithKline Beecham Biologicals' Hib vaccine, either mixed in one syringe and given in one single injection or given in two simultaneous injections into opposite limbs, as a booster vaccination at the age of 15 to 19 months to healthy children, previously primed with a three-dose primary vaccination course using the same vaccines in study DTPa-IPV 004.

6.1 Study Objectives

The primary objective of study DTPa-IPV 004 was to evaluate the immunological memory induced by the study vaccines during primary vaccination, as assessed through a booster response to all antigens contained in SB's combined DTPa-IPV and Hib vaccines, following a fourth dose in the second year of life.

The secondary objectives were to evaluate the persistence of antibodies to all antigens approximately one year after primary vaccination and to assess the reactogenicity of the vaccines when given as a fourth dose.

Criterion for evaluation of immunogenicity: serum antibody titers assessed in blood samples taken just prior to and one month after vaccination.

Reviewer's comment: *The criterion does not clearly specify how immunogenicity will be assessed. How are the pre and post vaccination serum antibody titers compared to assess immunogenicity?*

6.2 Study Design

Study DTPa-IPV 004 is an open-label randomized multicenter study that enrolled 131 healthy children aged 15 to 19 months into one of two groups in order to receive a booster vaccination of either the combined DTPa-IPV/Hib vaccine or the DTPa-IPV and Hib vaccines separately in opposite limbs.

In group 2 each subject received two vaccines -- one vial labeled ‘right’ and one ‘left’; the subject number was on both vials.

6.3 Statistical Evaluations

A total of 64 subjects were enrolled and considered eligible for inclusion in the analysis of reactogenicity and immunogenicity.

The number of vaccine doses followed by a report of symptoms (solicited and unsolicited) within the 4-day follow-up period and the nature of these symptoms (local or general) are presented in table 13. Symptom sheets were returned for all doses administered (100% compliance for reactogenicity reporting). All data obtained through diary cards or telephone contacts were included in the analysis of reactogenicity.

Table 13: Incidence and nature of symptoms after each vaccine and overall

N	Any Symptoms		General Symptoms		Local Symptoms			
					Left deltoid		Right Deltoid	
	n	%	n	%	N	%	n	%
64	56	87.5	41	64.1	48	75.0	24	37.5

N= total number of symptom sheets returned following vaccination
n = total number of symptom sheets reporting a symptom following vaccination.

Analysis of Immunogenicity
Percentages of subjects with anti-PRP antibody titres ≥0.15µg/ml, ≥0.5µg/ml, and ≥1.0µg/ml at the analysis points and the geometric mean anti-PRP antibody titres of all subjects tested before vaccination and one month after the booster dose are given in Table 14.

Table 14: GMTs of anti-PRP antibodies and distribution of anti-PRP titres

Timing				GMT	95% CI		≥0.15 mcg/ml		≥0.5 mcg/ml		≥1.0 mcg/ml	
	N	S+	%	value	LL	UL	n	%	n	%	n	%
Pre	63	45	71.4	0.254	0.196	0.330	45	71.4	17	27.0	8	12.7
PIV(d30)	64	64	100.0	47.779	36.891	61.881	64	100.0	64	100.0	64	100.0

N = number of subjects tested
Pre = prevaccination blood sample
PIV (d30) = blood sample taken approx one month after the booster dose = day 30.

Seropositivity rate immediately prior to vaccination was 71.4%, and had increased to 100% by one month after the booster dose. All subjects had titres ≥1µg/ml following the booster dose. GMTs rose from 0.254 to 47.779µg/ml from pre to post booster dose.

6.4 Reviewer's Comments

1. The study was conducted outside of the US and was not under FDA/CBER IND regulation. Hence, CBER did not review or concur on the protocol and the study report during and after the study.

2. The protocol did not specify immunogenic endpoints and criteria to evaluate the primary and secondary objectives.

3. The study is designed for subjects between 15-19 months of age, but all reported results for group 2 are for subjects between the ages of 16 -19 months

4. All analyses and reports are based on descriptive statistics results, which I was able to verify.

7. Study DTPa-HBV-IPV- 028

This study report is a modified report of the original clinical study report for study DTPa-HB-IPV-028 dated May, 1999. The analyses and data presented in this modified study report are limited to the group receiving DTPa-HBV-IPV co-administered with Hiberix at separate injection sites (study group 4 in the original study).

Study DTPa-HBV-IPV-028 was an open-label clinical study to assess the safety and reactogenicity of SB Biologicals' DTPa vaccine, co-administered with commercial Hib vaccine into opposite limbs, as compared to SB Biologicals' DTPa vaccine mixed with SB Biologicals' Hib vaccine, to SB Biologicals' DTPa-IPV vaccine mixed with SB Biologicals' Hib vaccine, and to SB Biologicals' DTPa-HBV-IPV vaccine co-administered with SB Biologicals' Hib vaccine into opposite limbs, when given as a booster dose to healthy children in their second year of life, previously primed with three doses of SB Biologicals' DTPa-HBV-IPV vaccine.

7.1 Study Objectives

The original objective in the study protocol was to assess and compare the safety and reactogenicity of the four booster vaccination regimens following primary vaccination with SB's DTPa-HBV-IPV vaccine.

The following primary and secondary objectives were stated for the modified study report within DTPa-HBV-IPV-028:

Primary objective

To demonstrate that SB's DTPa-HBV-IPV combined vaccine co-administered with SB's Hib vaccine in separate injections is not clinically significantly more reactogenic than commercial vaccines [Infanrix™ (SB's DTPa) and HibTITER™ (Lederle's PRPCRM$_{197}$) along with Polio Sabin™ (SB's Oral Polio)] in terms of incidence of "grade 3" solicited symptoms.

Secondary objective

To assess the safety and reactogenicity of four booster vaccination regimens following a primary vaccination course using SB's DTPa-HBV-IPV vaccine co-administered with Hib vaccines (from four different manufacturers) at separate injection sites.

7.2 Study Design

The study was an open-label, randomized, parallel group, multisite booster study with 4 groups with unbalanced allocation (1:3:2:2). Vaccination schedule: single booster dose with a 1 month follow-up.

Group 1 (control): SB's DTPa + Lederle's HibTITER™ + SB's OPV
Group 2: SB's DTPa/Hib + SB's OPV
Group 3: SB's DTPa-IPV/Hib
Group 4: SB's DTPa-HBV-IPV + SB's Hib

Analyses and data presented in this modified study report are limited to the group receiving DTPa-HBV-IPV co-administered with Hiberix at separate injection sites (study group 4).

7.3 Statistical evaluation

Primary endpoint

The primary endpoint of interest in study DTPa-HBV-IPV-028 was the proportion of subjects reporting any solicited symptoms graded 3 in intensity during the 4-day follow-up period after vaccination.

Secondary endpoint(s)

1. Proportions of subjects reporting any symptom (local or general, solicited or unsolicited) during the 4-day follow-up period after vaccination.
2. Proportions of subjects reporting any local symptom (solicited or unsolicited) during the 4-day follow-up period after vaccination.
3. Proportions of subjects reporting any general symptom (solicited or unsolicited) during the 4-day follow-up period after vaccination.
4. Incidence of each solicited local symptom during the 4-day follow-up period after vaccination (any intensity and with intensity rated as "grade 3," respectively).
5. Incidence of each solicited general symptom during the 4-day follow-up period after vaccination (any intensity, with intensity rated as "grade 3" and with relationship to vaccination assessed as "Probable (PB)" or "Suspected (SU)," respectively).
6. Incidence of unsolicited symptoms counted and classified by WHO preferred terms, during the 30-day follow-up period after vaccination.

Data Sets analyzed:

The primary analysis was based on the ATP cohort. The secondary analysis was based on the ITT cohort.

7.3.1 Analysis of Safety

The sponsor conducted the following descriptive analysis: the percentage of doses followed by a report of any symptom (local or general, solicited or unsolicited) and percentage of doses followed by at least one local (solicited or unsolicited) or general (solicited or unsolicited) symptom, for all doses documented, during the four-day follow-up period, calculated with their exact 95% CI. The percentage of subjects experiencing any solicited symptom regardless of intensity and solicited symptoms graded 3 in intensity was calculated, with the exact 95% CI, for each solicited symptom.

The primary analyses were based on the ATP cohort, and the primary variable considered for analysis was the proportion of subjects reporting at least one solicited symptom rated as grade 3 in intensity during the 4-day follow-up period following the booster vaccination. The incidence and nature of solicited symptoms graded 3 in intensity and reported during the 4-day follow-up period after the booster dose are presented in table 15.

Table 15: Incidence and nature of solicited symptoms graded 3 in intensity reported during the 4-day follow-up period after booster vaccination

	Any grade 3 solicited Symptom			Grade 3 solicited local Symptom			Grade 3 solicited general Symptom		
N	n	%	95% CI	n	%	95% CI	n	%	95% CI
359	46	12.8	9.5 – 16.7	26	7.2	4.8 – 10.4	24	6.7	4.3 – 9.8

N = number of documented doses;
n = number of documented doses followed by a specified symptom;
% = percentage of documented doses followed by a specified symptom

The incidence of all symptoms (solicited and unsolicited) and the nature of symptoms (local and general) reported over the 4-day follow-up period (days 0 to 3) are:

	Any Symptom			Local symptom			General symptom		
N	n	%	95% CI	n	%	95% CI	n	%	95% CI
359	263	73.3	68.4 – 77.8	158	44	38.8 – 49.3	234	65.2	60.0 – 70.1

N = number of documented doses
n = number of documented doses followed by a specified symptom
% = percentage of documented doses followed by a specified symptom

General symptoms were reported with a higher frequency than local symptoms. The incidences of local symptoms were similar between both injection sites; the DTPa containing vaccines seemed to induce slightly more local symptoms (37.9% with 95% CI of (32.8-43.1)) as compared to the Hib vaccine injection site (33.1% with 95% CI (28.3-38.3)). (Table 15 in the applicant's study report.)

7.3.2 Analysis of efficacy

Not applicable

Applicant's over all conclusion

The co-administration of a booster dose of SmithKline Beecham Biologicals' combined DTPa-HBV-IPV vaccine and Hiberix™ vaccine, was well tolerated and safe.

Reviewer's comment:

The primary objective of the study was "to demonstrate that SB's DTPa-HBV-IPV combined vaccine co-administered with SB's Hib vaccine in separate injections is not clinically significantly more reactogenic than commercial vaccines [Infanrix™ (SB's DTPa) and HibTITER™ (Lederle's PRPCRM197) along with Polio Sabin™ (SB's Oral Polio)] in terms of incidence of "grade 3" solicited symptoms." This objective was not demonstrated in the study.

7.4 Reviewer's comments

1. The study was conducted outside of the US and was not under FDA/CBER IND regulation. Hence, CBER did not review and concur on the protocol and the study report during and after the clinical trial or study.

2. The protocol of the study stated that the sample size determination would be based on the type of statistical tests to be used. However, the protocol does not specify the type of statistical test planned to be carried out.

3. The protocol and the study report do not specify the amount of increase to be considered as clinically significant in the proportion of subjects reporting at least one solicited symptom rated as grade 3 in intensity in the sample size and power calculation. The reviewer determined that the reported or planned power will rule out a 10% increase in proportion, but this is not reported as a planned clinically significant increase in the protocol.

4. On page 19 of the report, the primary objective is stated as "to demonstrate that SB's DTPa-HBV-IPV combined vaccine co-administered with SB's Hib vaccine in separate injections is not clinically significantly more reactogenic than commercial vaccines [Infanrix™ (SB's DTPa) and HibTITER™ (Lederle's PRPCRM197) along with Polio Sabin™ (SB's Oral Polio)] in terms of incidence of "grade 3" solicited symptoms." There was no statistical hypothesis set to assess this objective. No comparison is made between the proportion of subjects receiving SB's DTPa-HBV-IPV + Hib and the proportion of subjects receiving the commercial vaccines. The conclusion of the study given by the applicant does not demonstrate this objective.

5. I was able to verify the descriptive statistics results obtained by the applicant.

8. Study DTPa-HBV-IPV- 010

This section covers a review for the modified study report 217744/010 (DTPa-HBV-IPV-010).

The original study dated November 14, 1996 was an open-label clinical study to evaluate the immunogenicity and reactogenicity of SmithKline Beecham Biologicals' DTPa-HBV-IPV vaccine, co-administered with SmithKline Beecham Biologicals' Hib vaccine as two separate injections and given as a booster vaccination at the age of 15 to 18 months to healthy children, previously primed with three doses of SB Biologicals' DTPa-HBV-IPV vaccine and a commercially available Hib vaccine.

The modified study report is limited to analyses and data presented to the booster phase of the study.

8.1 Study Objectives:

The primary objective of study DTPa-HBV-IPV-010 was: to evaluate the persistence of antibodies to all antigens contained in SmithKline Beecham Biologicals' diphtheria−tetanus−acellular pertussis−hepatitis B−inactivated polio (DTPa-HBV-IPV) vaccine approximately one year after a primary vaccination course.

The secondary objectives were: to assess the immunogenicity and reactogenicity of a fourth booster dose of SmithKline Beecham Biologicals' combined DTPa-HBV-IPV vaccine; to evaluate the reactogenicity of a booster dose of SmithKline Beecham Biologicals' Hib vaccine.

8.2 Study Design

Study DTPa-HBV-IPV-010 was an open-label study with one group. No randomization of subjects was performed. All subjects enrolled in this study had previously participated in study DTPa-HBV-IPV-004 and had received a complete primary vaccination course of SmithKline Beecham Biologicals' DTPa-HBV-IPV vaccine co-administered with commercially available Hib tetanus conjugate vaccine as two separate injections in opposite limbs at 2, 4, and 6 months of age. Subjects in the present study were given the same subject number as in study DTPa-HBV-IPV-004. Each subject received only the vaccine labeled with his/her subject number.

8.3 Statistical Evaluation

In this modified report, analyses and data presented are limited to the booster phase of the study; hence, the statistical review is limited to the booster phase only.

Population group: Healthy children aged 15 to 18 months at the time of vaccination.

Number of subjects: Enrolled = 43
Reactogenicity analysis = 43
Immunogenicity analysis= 42

8.3.1 Analysis of Immunogenicity

The immunogenicity of the vaccine was investigated by measuring the humoral immune response to each vaccine antigen component, at approximately one month after vaccination.

Criteria for evaluation:

Measurement of serum titres of antibodies against each vaccine antigen component before, and one month after, booster vaccination.

The majority (>64%) of subjects vaccinated at 2, 4, and 6 months of age during study DTPa-HBV-IPV-004 were still seropositive for antibodies to each vaccine antigen at the time of the booster vaccination at 15 to 18 months of age. All vaccinees showed a booster response to all vaccine antigens indicating that effective priming for each of the vaccine antigens had occurred. Pre and post booster seropositivity rates (%) and GMTs were as follows:

			Seropositivity rates (%)		GMT*	
			Pre-booster	Post-booster	Pre-booster	Post-booster
Antibody	N	cut-off				
Diphtheria	42	≥0.1 IU/ml	64.3	100.0	0.185	8.051
Tetanus	42	≥0.1 IU/ml	92.9	100.0	0.338	7.568
PT	42	≥5 EL.U/ml	76.2	100.0	7.5	130.3
FHA	40	≥5 EL.U/ml	95.0	100.0	34.2	638.7
PRN	42	≥5 EL.U/ml	81.0	100.0	13.3	381.0
HBs	42	≥10 mIU/ml	92.9	100.0	108	6736
Polio type 1	41	≥8 VN dil	78.0	100.0	26.2	1264.0
Polio type 2	41	≥8 VN dil	90.2	100.0	38.4	1979.1
Polio type 3	41	≥8 VN dil	95.1	100.0	163.4	4197.2
PRP	42	≥0.15 µg/ml	76.2	100.0	0.457	59.065
PRP	42	≥1.0 µg/ml	35.7	97.6	-	-

*Units: IU/ml for diphtheria and tetanus; EL.U/ml for PT, FHA and PRN; mIU/ml for HBs; VN dil for poliovirus types 1, 2 and 3; µg/ml for PRP

Reviewer's comment: *One of the criteria for immunogenicity "the percentage of subjects with a protective (or seropositive) level before and after vaccination" is not statistically significant for the following antibodies: tetanus (p-value=0.2396), FHA (p-value=0.4739), HBs (p-value=0.2396), polio type 2 (p-value=0.1241), and polio type 3 (p-value=0.474). The proportion of subjects with titers ≥ the cut-off for each of these antibodies before vaccination is not statistically different (or less) than the proportion after vaccination.*

8.3.2 Analysis of Reactogenicity

Data concerning solicited and unsolicited signs and symptoms from the entire symptom sheets returned to the applicant are reported (compliance 100%). The overall incidence and nature of symptoms reported during the four-day follow-up period was as follows:

	Local Symptoms				General Symptoms		Without Symptoms	
	Hib		DTPa-HBV-IPV					
N	n	%	n	%	n	%	n	%
43	14	32.6	28	65.1	30	69.8	6	14.0

N = total number of doses administered with a symptom sheet returned
n = number of doses with the specified characteristic

Overall, no symptoms (including local, general, solicited, or unsolicited) were reported for 14.0% of the doses administered within the four days of the booster dose.

The incidence of solicited local symptoms reported over the four-day follow-up period was as follows:

Symptoms	N →	43			
		Hib		DTPa-HBV-IPV	
		n	%	n	%
Pain	all	13	30.2	16	37.2
	grade 3*	0	0.0	0	0.0
Redness	all	1	2.3	18	41.9
	>20mm	1	2.3	7	16.3
Swelling	all	4	9.3	21	48.8
	>20mm	3	7.0	15	34.9

*grade 3 = pain that prevents normal, everyday activities

Fewer local reactions were reported at the Hib injection site as compared to the DTPa-HBV-IPV injection site. The majority of the local and general reactions reported were mild to moderate in intensity.

All seven (16.3%) cases of fever reported occurred within the first 48 hours after vaccination.

Only one (2.3%) case of fever >39.5°C was reported. Twenty-four verbatim reports of unsolicited symptoms were received for 13 subjects. Of these, eight were considered to be related to the vaccination, all of which were injection site reactions. No severe unsolicited symptoms were reported. No serious adverse events were reported by the parents or guardians of subjects during the course of the study.

GSK's overall conclusions

- The majority (>64%) of subjects vaccinated with SB Biologicals´ DTPa-HBV-IPV vaccine and a commercially available Hib vaccine at approximately 2, 4, and 6 months of age were still seropositive for antibodies to each vaccine antigen at the time of booster vaccination at 15-18 months of age.
- Following booster vaccination, all subjects were seropositive to each of the pertussis and polio antigens. All subjects had protective (≥ 10 mIU/ml) anti-HBs antibody titres, and anti-diphtheria and anti-tetanus titres ≥ 0.1 IU/ml. All subjects had anti-PRP antibody titres ≥ 0.15µg/ml and 97.6% of subjects had anti-PRP antibody titres ≥ 1.0µg/ml. The GMTs against each vaccine antigen increased substantially from pre to post booster dose.

- The majority of local and general reactions reported were mild to moderate in intensity. No serious adverse events were reported. The overall safety profile of SB Biologicals´ DTPa-HBV-IPV and Hib vaccines was considered to be acceptable by the investigator, when administered simultaneously as a booster dose in the second year of life.

8.4 Reviewer's comment

1. One of the criteria for immunogenicity "the percentage of subjects with a protective (or seropositive) level before and after vaccination" is not statistically significant for the following antibodies: tetanus (p-value=0.2396), FHA (p-value=0.4739), HBs (p-value=0.2396), polio type 2 (p-value=0.1241), and polio type 3 (p-value=0.474). The proportion of subjects with titers ≥ the cut-off for each of these antibodies before vaccination is not statistically different (or less) than the proportion after vaccination.
2. The indication/study population specified in the protocol and the study report is booster vaccination at 15 to 18 months of age. But all subjects included in the study were in the age range 16 to 18 months (Mean age = 16.9 months, Minimum age =16 months, Maximum age =18 months).

9. Study DTPa-HBV-IPV- 035

Subjects in booster study DTPa-HBV-IPV-35 received primary vaccination in two studies DTPa-HBV-IPV-011 and DTPa-HBV-IPV-016. In study DTPa-HBV-IPV-011 subjects received either Hiberix or US licensed Hib vaccines as primary vaccination. In study DTPa-HBV-IPV-016 subjects did not receive any US licensed Hib vaccines. Study DTPa-HBV-IPV-035 is included in this BLA to document the use of Hiberix as a booster dose after priming with a US licensed Hib vaccine. Therefore, only data from subjects primed in study DTPa-HBV-IPV-011 are of interest.

The modified interim study report for study DTPa-HBV-IPV-035 presents data generated in subjects primed in study DTPa-HBV-IPV-011. Endpoints and data presented are limited to the group receiving DTPa-HBV-IPV co-administered with Hiberix at separate injection sites (study group 3) and, with regard to immunogenicity, to the response to PRP only.

The original clinical study report is dated June 2, 1999 and report errata are dated December 22, 1999.

Study DTPa-HBV-IPV-035 was designed to evaluate the reactogenicity and immunogenicity of formulations A and B of SB's Hib tetanus conjugate vaccine, when co-administered with SB's DTPa-HBV-IPV vaccine either mixed in a single syringe or in separate injections, as a booster dose. It was entitled as "a phase II randomized booster vaccination study of one dose of SB Biologicals' DTPa-HBV-IPV vaccine, co-administered with two formulations of SB Biologicals' Hib conjugate vaccine, either mixed in one syringe or injected simultaneously in two concomitant injections into opposite limbs at the same visit, in healthy children who previously participated in study 217744/011 (DTPa-HBV-IPV-011) or Groups 1, 2 and 3 of study 217744/016 (DTPa-HBV-IPV-016)."

9.1 Study Objectives

Primary objective:

To evaluate and compare the safety and reactogenicity of the DTPa-HBV-IPV vaccine mixed with two formulations of Hib conjugate vaccine.

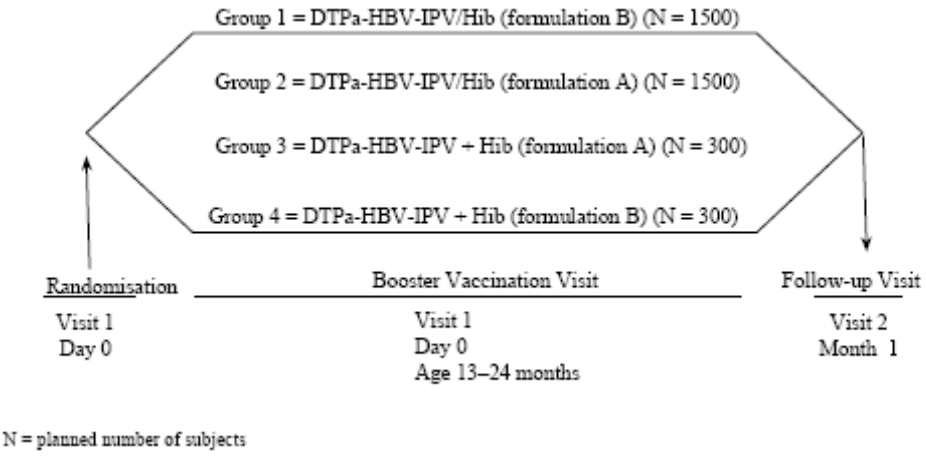
Secondary objective:

To compare the reactogenicity of the DTPa-HBV-IPV vaccine mixed with Hib to separate injections of the two vaccines, for both formulations of the Hib vaccine; to evaluate and compare the immunogenicity of the Hib components between the two groups receiving the mixed vaccines and to separate injection of the respective formulation of the Hib vaccine; to evaluate the immunogenicity of all other vaccine components in terms of specific antibodies; to evaluate the persistence of antibodies to all vaccine components induced during primary vaccination.

9.2 Study Design

Study DTPa-HBV-IPV-035 was a randomized, parallel group, multisite booster study with 4 groups with unbalanced allocation (5:5:1:1), performed in a double-blind manner for the two Hib vaccine formulations.

The diagram below gives an overview of the study design:



N = planned number of subjects

9.3 Statistical Evaluation

Data presented in the modified study report are limited to the group receiving DTPa-HBV-IPV co-administered with Hiberix at separate injection sites (study group 3) and, with regard to

immunogenicity, to the response to PRP only. The number of subjects in the ATP cohort for the primary analysis (safety) in this group was 145, and ATP cohort for immunogenicity: 56 subjects.

An interim analysis was performed on subjects primed in study DTPa-HBV-IPV-011 and who had completed their booster vaccination course by December 31, 1998.

Statistical method:

The interim analysis was restricted to descriptive analyses

Primary endpoint:

Occurrence, nature, and relationship to vaccination of solicited symptoms in each group.

Secondary endpoints:

- Occurrence of any local symptoms within 4 days after vaccination.
- Occurrence of any general symptoms within 4 days after vaccination.
- Occurrence of any symptoms within 4 days after vaccination.
- Occurrence of unsolicited symptoms within 30 days after vaccination.
- Occurrence of serious AEs throughout the entire study up to and including 30 days post-vaccination.
- Antibody titres to PRP, before and one month after the booster dose of the study vaccines
- Ser**o**protection defined as: Anti-PRP antibody titres ≥0.15 mcg/ml and ≥1.0 mcg/ml before and one month after the booster dose of the study vaccines.

9.3.1 Analysis of reactogenicity and safety

This interim analysis of safety and reactogenicity was restricted to descriptive analyses.

The primary analyses were based on the ATP cohort.

Descriptive analysis: The number and percentage with exact 95 % Confidence Interval (CI) of documented doses documenting at least one symptom (local or general, solicited or unsolicited), at least one general symptom (solicited or unsolicited) and at least one local symptom (solicited or unsolicited) reported during the solicited follow-up period were computed.

Criteria for evaluation:

Assessment of solicited local symptoms (pain, redness, and swelling at the injection site) and general symptoms (fever, fussiness/irritability, vomiting, diarrhea, loss of appetite, restlessness, and sleepiness) during a four-day follow-up period after vaccination.

Reactogenicity and safety results

The incidence of all symptoms (solicited and unsolicited) and the nature of symptoms (local and general) reported over the 4-day follow-up period (days 0 to 3) after the booster vaccination are presented in the following table (table 14 on page 41 in applicant's report).

Group	N	All symptoms			General symptoms			Local* symptoms		
		n	%	95%C.I.	n	%	95%C.I.	n	%	95%C.I.
3	145	119	82.1	74.8; 87.9	104	71.7	63.7; 78.9	92	63.4	55.1; 71.3

Group 3: boosted with DTPa-HBV-IPV + Hib (formulation A)
This table includes both solicited and unsolicited symptoms reported on symptom sheets during the 4 day follow-up period.
*Local: Number of documented doses reporting at least one local symptom whatever the number of injections.
For local symptoms and multiple injections, a symptom was counted once even if reported on multiple sites.
N = number of subjects with at least one documented dose
Documented dose = at least one symptom sheet completed and/or at least one unsolicited symptom reported.
n = number of subjects presenting at least one type of symptom
% = percentage of subjects presenting at least one type of symptom
95% CI: Exact 95% confidence interval

General symptoms were reported with a higher frequency than local symptoms. As seen in the following table (table 15 on page 41 of the applicant's report), the incidence of local symptoms at the DTPa-HBV-IPV vaccine injection site was slightly higher than incidence at the Hib vaccine injection site.

Incidence of local symptoms reported after each treatment during the 4-day follow-up period after booster vaccination (ATP cohort for reactogenicity analysis)

Group	N	DTPa-HBV-IPV/Hib			DTPa-HBV-IPV			Hib		
		n	%	95%C.I.	n	%	95%C.I.	n	%	95%C.I.
3	145	-	-	-	79	54.5	46.0; 62.8	78	53.8	45.3; 62.1

Group 3: boosted with DTPa-HBV-IPV + Hib (formulation A)
This table includes both solicited and unsolicited symptoms reported on symptom sheets during the 4 day follow-up period.
N = number of subjects with at least one documented dose
Documented dose = at least one symptom sheet completed and/or at least one unsolicited symptom reported.
n = number of subjects presenting at least one type of symptom
% = percentage of subjects presenting at least one type of symptom
95% CI: Exact 95% confidence interval

Redness (37.2%) at the injection site was the most common solicited local symptom. Fever (=rectal temperature ≥38°C (≥100.4°F) or axillary, oral and tympanic temperature ≥37.5°C (≥99.5°F)) was the most frequently reported solicited general reaction with 42.8% of subjects reporting the symptom, followed by fussiness with 39.3%.

During the follow-up period (days 0-30), 88 unsolicited symptoms were counted and classified by WHO Preferred Terms. One symptom was graded 3 in intensity.

Serious Adverse Events*:*
No SAEs were reported

Withdrawals due to AE/SAE:
There were no withdrawals due to serious or non-serious adverse events

9.3.2 Analysis of immunogenicity

The interim analysis of immunogenicity was restricted to descriptive analyses. The primary analyses were based on the ATP cohort.

The seroprotection rate, at each time point (defined as the proportion of subjects with anti-PRP antibody titres ≥ 0.15 mcg/ml and ≥ 1.0 mcg/ml based on the reverse cumulative distribution curve of antibody titres), was generated for the ATP cohort for post-booster immunogenicity analysis.

The seroprotection rates and GMTs with their 95% CI for anti-PRP antibodies are shown in the following table (table 35 on page 48 of applicant's report).

			≥0.15 mcg/ml				≥1.0 mcg/ml				GMT		
Group	Timing	N	n	%	95% CI		n	%	95% CI		mcg/ml	95% CI	
3	Pre	56	54	96.4	87.7	99.6	29	51.8	38.0	65.3	1.189	0.882	1.603
	Post	56	56	100	93.6	100	54	96.4	87.7	99.6	53.642	35.730	80.533

Individual immunogenicity data can be found in Appendix Table IIIA
Group 3: boosted with DTPa-HBV-IPV + Hib (formulation A)
N = number of subjects with available results
n / % = number / percentage of subjects with titres within the specified range
Pre = Pre-vaccination blood sample obtained immediately before the booster dose
Post = Post vaccination blood sample obtained one month after the booster dose
GMT = Geometric mean titre

One month after the booster dose all subjects had anti-PRP antibody titres ≥ 0.15 mcg/ml and 96.4% subjects had anti-PRP antibody titres ≥ 1.0 mcg/ml. Anti-PRP antibody GMTs increased 45-fold in group 3 from pre to post booster vaccination.

Reviewer's comment: *There is no statistical significance between the percentage of subjects who had anti-PRP antibody titer ≥ 0.15 mcg/ml pre and post booster vaccination.*

GSK's overall conclusion

- One month after the booster dose, 96.4% of subjects had anti-PRP antibody concentrations ≥ 1.0 mcg/ml.
- SB's combined DTPa-HBV-IPV vaccine co-administered with SB's Hib vaccine (Hiberix) co-administered in separate injections is safe when given in the second year of life.

9.4 Reviewer's Comment

1. The study was conducted outside of the US and was not under FDA/CBER IND regulation. Hence, CBER did not review and concur on the protocol and the study report during and after the trial.

2. All statistical analyses in this study are descriptive analysis. I verified the results and conclusions drawn.

3. I performed immunogenicity analysis of the ITT cohort and obtained consistent results with those obtained from the analysis of the ATP cohort, ensuring the deviations from the protocol were not treatment related and did not appear to lead to bias in the results.

10. Conclusions and Recommendations

Considering the lack of opportunity to provide feedback and suggestions to the applicant's proposed study, many of these studies provided within the BLA still appear to support the applicant's claim that this product appears to be safe and to elicit adequate immune response.