# *Infanrix*$_{DTPa}$-HepB-IPV™

(DTPa-HepB-IPV vaccine)

Briefing Document

Vaccines and Related Biological Products
Advisory Committee Meeting

March 7, 2001

SmithKline Beecham Biologicals
(a GlaxoSmithKline Company)

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# 1.0 Introduction

## 1.1 List of Abbreviations

Please see Appendix I for a list of abbreviations that may be used in this document.

## 1.2 Introduction to Product & Indication

SmithKline Beecham Biologicals (SBB), a GlaxoSmithKline Company (GSK) in Rixensart, Belgium (US License Number 1090) has developed a liquid vaccine combining diphtheria and tetanus toxoids, acellular pertussis, hepatitis B, and inactivated poliovirus types 1, 2 and 3 antigens.

***Product Names***

Proposed trade name:

***Infanrix*$_{\text{DTPa}}$-HepB-IPV™**

Proposed proper/generic name:

Diphtheria and Tetanus Toxoids, Acellular Pertussis, Hepatitis B (Recombinant), Inactivated Poliovirus Vaccine

Abbreviation used in this document:

DTPa-HepB-IPV

***Indication***

Active immunization against diphtheria, tetanus, pertussis (whooping cough), all known subtypes of hepatitis B virus, and poliomyelitis caused by poliovirus types 1, 2, and 3 as a three-dose primary vaccination series in infants and children 6 weeks to 7 years of age (prior to the seventh birthday).

An indication for fourth dose following primary series is not being sought at this time. The language in the indication providing for immunization prior to the seventh birthday is intended to allow for catch-up primary immunization.

***Components of the Combination & Marketing Status of Related Products***

The components of the DTPa-HepB-IPV vaccine are included, individually or in combination, in products that are licensed and commercially available in numerous markets around the world, including the U.S. (DTPa and HepB; see Appendix II for listings).

**DTPa**

- Identical to U.S.-licensed *Infanrix*® (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed)

**Hepatitis B**

- Identical to U.S.-licensed *Engerix-B*® (Hepatitis B Vaccine, Recombinant), with one additional, final purification step prior to adsorption

**Inactivated Poliovirus Vaccine (IPV)**

- Manufactured by SmithKline Beecham Biologicals (SBB) - manufacturing process is similar and antigen content (and virus strains) identical to U.S.-licensed IPOL® (Aventis Pasteur).

- Combines virus strains Type 1, Type 2 and Type 3

- Extensive clinical and market experience for IPV in licensed combinations in non-US markets (see Appendix II)

For clarification throughout the document, "+" indicates concomitant administration of vaccines at separate sites and "/" indicates combined administration in a single injection after extemporaneous mixing of vaccines, and "-" indicates that antigens are combined in the same liquid combination.

***Chemistry Overview & Product Presentation***

- White turbid suspension for injection
- Quantitative Composition – See Table 1
- Monodose – 0.5 mL
- 3 mL glass vials or 1 mL prefilled syringe (Tip-Lok®)

**Table 1: DTPa-HepB-IPV Vaccine Composition (per 0.5 mL dose)**

| NAMES OF INGREDIENTS | QUANTITY (per dose, 0.5 mL) |
|---|---|
| **Active substances** | |
| 1. Pertussis toxoid (PT), adsorbed | 25 µg |
| 2. Filamentous haemagglutinin (FHA), adsorbed | 25 µg |
| 3. Pertactin (69kDa Outer Membrane Protein – PRN), adsorbed | 8 µg |
| 4. Diphtheria toxoid (D), adsorbed | ≥ 2 U/mL or 25 Lf |
| 5. Tetanus toxoid (T), adsorbed | ≥ 2 U/mL or 10 Lf |
| 6. r-DNA Hepatitis B surface antigen (HBsAg), adsorbed | 10 µg |
| 7. Inactivated Poliovirus Type 1 | 40 DU |
| 8. Inactivated Poliovirus Type 2 | 8 DU |
| 9. Inactivated Poliovirus Type 3 | 32 DU |
| **Excipients** | |
| 1. 2-phenoxyethanol | 2.5 mg |
| 2. Sodium Chloride | 4.5 mg |
| 3. Water for injections | 0.5 mL |
| **Adjuvants** | |
| Aluminum as salts | 0.7 mg |

Note: No detectable thimerosal in the final product

## 1.3 Introduction to Preclinical & Clinical Information

### 1.3.1 Preclinical Summary

Preclinical toxicology and pharmacology studies were performed to examine the safety and immunogenicity of the components as they are contained in the combination vaccine. The active ingredients and excipients used in the manufacture of DTPa-HepB-IPV vaccine are well known. They are used in other SB Biologicals' US-licensed vaccines: *Infanrix*®, *Engerix-B*®, as well as Infanrix-based combinations licensed in other markets, e.g. Infanrix™ -HepB, Infanrix™-IPV/Hib, *Infanrix*™-PeNTa (DTPa-HepB-IPV) and *Infanrix*™-HeXa (DTPa-HepB-IPV/Hib admixed). The latter two were recently licensed via the centralized procedure in all 15 member states of the European Union and several additional countries (see also Appendix II).

Toxicological and pharmacological (immunogenicity) studies were performed and were in compliance with relevant sections of Title 21 of the Code of Federal Regulations and the NIH Minimum Requirements documents, as well as internal SB Biologicals Standard Operating Procedures.

### 1.3.2 Clinical Summary

Clinical trials conducted in support of the BLA, currently under review by FDA, were designed to demonstrate that the DTPa-HepB-IPV vaccine is safe and immunogenic when administered as a three dose primary series in infants.

In accordance with the *FDA Guidance for Industry For Evaluation of Combination Vaccines for Preventable Diseases: Production, Testing and Clinical Trials (April 1997*) and in support of the proposed indication and labeling the following critical objectives were included in the various clinical studies submitted in the BLA:

***Establish the Efficacy/Immunogenicity of the combination product:***

- Rule out important differences between the immune response elicited by each antigen in the combined vaccine as compared to the antigens administered separately and simultaneously as US-licensed vaccines (efficacy established by a bridge via immunogenicity for each component of the combination).

- Evaluate the immunogenicity of the candidate vaccine and lack of clinically significant interactions when administered simultaneously at separate sites with U.S.-licensed vaccines anticipated to be given on the same schedule (i.e. *Haemophilus influenzae* type b conjugate vaccine)

  *Note: Prevnar™ [Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM 197)] was not routinely recommended for vaccination in infants, nor commercially available at the time of submission of the Biologics License Application (BLA) for DTPa-HepB-IPV*

- Demonstrate clinical consistency of production lots of the candidate vaccine

- Demonstrate similar immunogenicity (via clinical bridging study) of two sequential series of production lots following a major manufacturing change (i.e. bridge used to demonstrate no relevant impact of the manufacturing change on immunogenicity)

- Compare the immunogenicity of the hepatitis B surface antigen (HBsAg) when given in the combination at 2, 4, and 6 months of age with that of the US-licensed regimen for hepatitis B vaccination (0, 1 and 6 months)

***Establish the safety of the combination product:***

- Rule out important differences in the safety and reactogenicity of the combined vaccine as compared to the antigens administered concomitantly at separate injection sites as U.S.-licensed vaccines

- Rule out important differences in the safety and reactogenicity of the combined vaccine when administered as a three dose primary series following a dose of hepatitis B vaccine given at or shortly after birth, as compared to a three dose primary series in the absence of the birth dose of hepatitis B vaccine.

Section 2.0 discusses the resultant data.

***Manufacturing Changes & Key to Product Lot Series***

A total of 13 production lots of SBB DTPa-HepB-IPV vaccine were used in the clinical studies included in the license application. During the clinical development and just following completion of the study DTPa-HepB-IPV 044, manufacturing changes were made to the product as an ongoing effort for process improvement and to ensure adequate capacity for the market. Changes and corresponding product lot series designations (as used throughout this document) as well as the approach to bridging between lot series is indicated in Table 2. The Third Lot series is intended for commercial launch.

**Table 2: Manufacturing Changes & Product Lot Series**

| **Lot Series Designation** | **Bridging Data** | **Usage** |
|---|---|---|
| First Lot Series | NA | Clinical Studies including study 044* (for bridging) |
| Second Lot Series | Clinical Bridge 044 (to First Lot Series) | Bridging & Consistency study 044* |
| Third Lot series | Technical Bridge (to Second Lot Series) | Commercial Launch (U.S. Market) |

*044 = study DTPa-HepB-IPV-044 conducted in U.S.

# 2.0 Clinical Information

## 2.1 Characterization of Immune Response – Clinical Serology

Serological methods utilized to characterize the immune responses in sera drawn from immunized subjects in the clinical studies were fully validated and shown to be sensitive, specific and reproducible as appropriate. For antigens in the combination which are also included in U.S.-licensed products (e.g. DTPa, HepB), assays employed in these studies were similar to those assays previously approved by FDA under the existing license applications for the individual products *(Infanrix & Engerix-B*).

A listing of the validated serological assays and the cut-offs employed to measure the immune response to the antigens contained in the DTPa-HepB-IPV vaccine is provided in Table 3.

**Table 3: Serological Methods Employed in Clinical Studies**

| Immunizing Antigen | Serological Method | Cut-Off |
|---|---|---|
| Diphtheria Toxoid (D) | ELISA | 0.1 IU/mL |
| Tetanus Toxoid (T) | ELISA | 0.1 IU/mL |
| Pertussis Toxoid (PT) | ELISA | 5 EL.U/mL |
| Filamentous Haemagglutinin (FHA) | ELISA | 5 EL.U/mL |
| Pertactin (PRN) | ELISA | 5 EL.U/mL |
| Hepatitis B surface antigen (HBsAg) | RIA* | 10 mIU/mL |
| Poliovirus (types 1, 2, 3) (IPV) | Neutralization cell culture | 1/8 |
| PRP | RABA/ELISA | 0.15 µg/mL |

*US-licensed, commercial test kit

## 2.2 Summary of Clinical Trial Results

### 2.2.1 Overview of Studies in Support of Indication – See Table 4

***Schedule***

- In four studies (DTPa-HepB-IPV-001, DTPa-HepB-IPV-005, DTPa-HepB-IPV-011, and DTPa-HepB-IPV-016) vaccination was performed at approximately monthly intervals with the first dose given at approximately 12 weeks of age (3, 4, 5 month schedule).

- In four trials (DTPa-HepB-IPV-002, 004, 015, and 044), vaccine was administered at approximately 2, 4, and 6 months of age (with the first dose at 6-12 weeks of age).

- Two studies evaluated vaccination at 3, 4.5, and 6 months of age (DTPa-HepB-IPV-012 and 019) and one study (DTPa-HepB-IPV-017) evaluated a schedule of 2, 3 and 4 months of age.

***Lot-to-lot Consistency***

- Two studies (DTPa-HepB-IPV-005 and 044) evaluated the consistency (3 lots) with respect to safety and immunogenicity of this vaccine in a three dose primary vaccination course following a 3, 4, 5 (study 005; First Lot series) or a 2, 4, and 6 month schedule (study 044; Second Lot series).

***Comparison to Licensed Separate Injections - Immunogenicity***

- One study (DTPa-HepB-IPV-015) conducted in the U.S. on a 2, 4, and 6 month schedule compared three doses of the DTPa-HepB-IPV vaccine to separate administration of US-licensed DTPa, HepB, Hib and OPV vaccines. In addition, comparison to a US-licensed IPV vaccine (IPOL®) was performed.

***Co-administration***

- In most studies, the DTPa-HepB-IPV vaccine was administered simultaneously at separate sites with a Hib vaccine and the response to each antigen administered was evaluated. Moreover, co-administration was specifically addressed in study DTPa-HepB-IPV-012, in which four Hib vaccines (manufactured by SBB, Aventis Pasteur, Lederle and Merck) were given.

- Note: Prevnar™ [Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM 197)] was not routinely recommended for vaccination in infants, nor commercially available at the time of submission of the Biologics License Application (BLA) for DTPa-HepB-IPV.

***Safety***

- The majority of the safety database for the file was derived from a large safety study performed in Germany (DTPa-HepB-IPV-011) in which nearly 5500 infants received 3 doses of either DTPa-HepB-IPV vaccine (N = 4695) or separate injections of DTPa and Hib vaccines, along with OPV vaccine (N = 776). In total, more than 7,000 infants have received at least one dose of DTPa-HepB-IPV vaccine in the context of 12 clinical trials.

***Birth Dose of Hepatitis B and Schedule Change for Hepatitis B Vaccination***

- A thirteenth study (DTPa-HepB-IPV/Hib-003) conducted in the US evaluated the impact of a dose of hepatitis B vaccine given at or shortly after birth on the safety of a subsequent primary course of DTPa-HepB-IPV vaccine extemporaneously mixed and given in a single injection with Hib tetanus toxoid conjugate vaccine manufactured by SB Biologicals. This study was intended to support the safety of the DTPa-HepB-IPV following a birth dose of hepatitis B as well.

- A fourteenth study (DTPa-HepB-030) was a supportive study that evaluated a change in schedule for the HepB (from 0, 1, 6 months) to 2, 4, 6 months as it is administered as a part of the DTPa-HepB-IPV vaccine. The composition of the DTPa-HepB vaccine used in that study was similar to the DTPa-HepB-IPV vaccine, except for the IPV component.

## Table 4: Summary of Studies in Support of SBB's DTPa-HepB-IPV vaccine

| DTPa-HepB-IPV Study (study type) | Country | Schedule (months of age) | Comparator | Objective (s) | # Receiving DTPa-HepB-IPV / Comparator |
|---|---|---|---|---|---|
| 001 (P) | Turkey | 3, 4, 5 | DTPa-HepB + IPV | Feasibility | 20 / 20 |
| 002 (P) † | Finland | 2, 4, 6 | N.A. | Feasibility | 30 / 0 |
| 004 (P) † | Canada | 2, 4, 6 | N.A. | Feasibility | 50 / 0 |
| 005 (S) † | Belgium | 3, 4, 5 | DTPa-HepB-IPV (+ OPV with 3rd dose) | Lot Consistency (First Lot series) | 567 / 0 |
| 011 (PV) † | Germany | 3, 4, 5 | DTPa + Hib + OPV | Safety vs. to US-licensed sep. injections | 4695 / 776 |
| 012 (S) † | Lithuania | 3, 4.5, 6 | N.A. | Hib Co-administration | 549 / 0 |
| 015 (PV) † | USA | 2, 4, 6 | DTPa-HepB-IPV x 2, DTPa-HepB + OPV; DTPa-HepB + IPV; DTPa + HepB + OPV | Safety & Immuno vs. US-licensed separate injections; Hib Co-administration | 200 / 200 |
| 016 (S) † | Germany | 3, 4, 5 | DTPa-HepB-IPV/Hib; DTPa-IPV/Hib + HepB | Safety & Immuno | 184 / 368 |
| 017 (S) † | France | 2, 3, 4 | DTPa-HepB-IPV/Hib; DTPa-IPV/Hib + HepB | Safety & Immuno | 29 / 180 |
| 019 (S) | Estonia | 3, 4.5, 6 | DTPa-HepB + IPV | Safety & Immuno | 60 / 60 |
| 030 (S) † | Moldova | 1.5, 2.5, 3.5 | DTPw-IPV/Hib + HepB (Birth dose HepB) | Safety after birth dose HepB | 160 / 160 |
| 044 (PV) † | USA | 2, 4, 6 | DTPa-HepB-IPV | Lot consistency*; Manufacturing Bridge** | 484 / 0 |
| DTPa-HepB-IPV/Hib-003 (S) | USA | 2, 4, 6 | DTPa-HepB-IPV/Hib vs. DTPa-HepB-IPV/Hib following HepB at birth | Safety after birth dose HepB | NA♣ |
| DTPa-HepB-030 (S) † | USA | 2, 4, 6 | DTPa + OPV at 2, 4, 6 months HepB at 0, 1, 6 months | Schedule Change HepB | NA♣ |
| | | | | TOTAL | 7028 / 1764 |

Study Type: P = Pilot, PV = Pivotal, S = Supportive N.A. = Not applicable *Second Lot series ** First to Second Lot Series

♣All of the above studies were conducted using SBB formulation of DTPa-HepB-IPV vaccine with the exception of study DTPa-HepB-IPV/Hib-003 in which the combined DTPa-HepB-IPV was given after extemperaneous mixing with SBB Hib vaccine, and study DTPa-HepB-030 which was conducted using SBB formulation of DTPa-HepB vaccine

†Hib vaccine coadministered at a separate site

### 2.2.2 Overall evaluation of the immunogenicity of the SBB DTPa-HepB-IPV vaccine

#### *2.2.2.1 Introduction*

Immunogenicity data from a total of 11 clinical studies evaluating the DTPa-HepB-IPV product, conducted in 10 countries (including the US), were submitted. In the twelfth study (DTPa-HepB-IPV-011) immunogenicity was not evaluated (i.e. this was a "safety only" study). In an additional study that evaluated a change in schedule for the HepB component when given as part of SBB's DTPa-HepB vaccine, no subject received the DTPa-HepB-IPV vaccine. In another study (DTPa-HepB-IPV/Hib-003), in which the DTPa-HepB-IPV was extemporaneously mixed and given in one single injection with Hib tetanus toxoid conjugate vaccine, safety of a 3 dose primary vaccination series following a birth dose of hepatitis B vaccine was evaluated.

A total of 3321 subjects (2233 receiving SBB DTPa-HepB-IPV candidate vaccine) were enrolled in the 11 clinical studies. Of the 3145 subjects (2143 receiving SBB DTPa-HepB-IPV candidate vaccine) with serological data available, 2845 (1918 receiving SBB DTPa-HepB-IPV candidate vaccine) were included in the ATP analysis of immunogenicity.

The SBB DTPa-HepB-IPV vaccine was immunogenic for all vaccine antigens in all study populations when administered as a three dose primary series according to a variety of vaccination schedules beginning as early as 6 weeks of age.

#### *2.2.2.2 Assessment of Immunogenicity*

Serum samples for measurement of the antibody response following vaccination were generally obtained before vaccination and approximately one month after the third vaccine dose.

#### *2.2.2.3 Methods*

All immunogenicity analyses in this briefing document are based on the According-to-Protocol (ATP) cohort for immunogenicity. The main reason for excluding a subject from the ATP cohort of immunogenicity was departure from the visit schedule according to pre-specified criteria.

The following post-vaccination immunogenicity parameters were investigated:

- "Seroprotection" rates, i.e., the percentages of infants with antibody titers equal to or above the assay cut-off, which for anti-diphtheria, anti-tetanus anti-HBs and anti-polio antibodies were set such that subjects who had titers above the cut-off could be considered to be protected from disease (see Table 5).

- Vaccine response rates, i.e. the percentages of infants fulfilling the criteria for vaccine response to each pertussis antigen (PT, FHA, and PRN). A vaccine response was defined as antibody titers equal to or above the assay cut-off (5 EL.U/mL) in subjects who were seronegative prior to vaccination and at least maintenance of pre-vaccination antibody titers in those who were seropositive prior to vaccination.

- Geometric mean antibody titers for each type of antibody.

- The distribution of antibody titers (plotted as reverse cumulative distribution curves).

The primary endpoints were seroprotection rates for anti-D, anti-T, anti-HBs and anti-polio 1, 2 and 3, and vaccine response rates and GMTs for the pertussis antigens (PT, FHA, PRN). All other endpoints were secondary.

The statistical methodology used to evaluate the immunogenicity of the study vaccine evolved during clinical development, from testing of the null hypothesis of no difference between vaccination groups in the earlier studies to testing for non-inferiority or equivalence in later studies (ICH E-9 Statistical principles for clinical trials, Final, February, 1998: Section 3.3.2).

The clinical limits defining non-inferiority of the SBB DTPa-HepB-IPV vaccine relative to a control, and consistency between lots of the SBB DTPa-HepB-IPV vaccine, were set as follows:

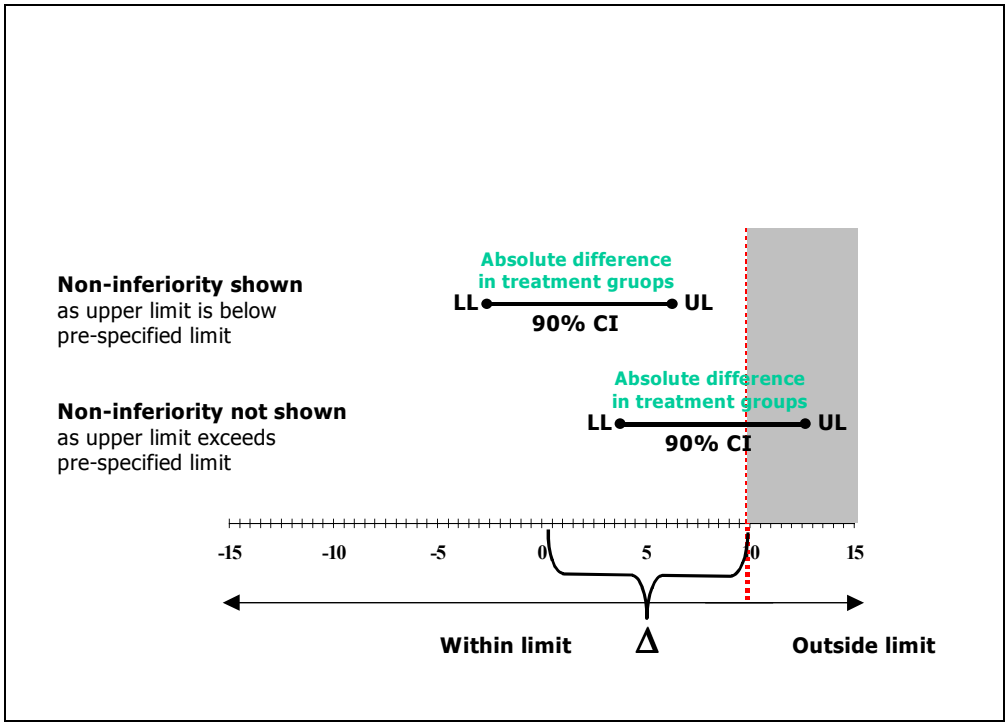
**Table 5: Clinical limits defining non-inferiority**

| **Seroprotection/ vaccine response rate** | **Max difference (Δ)** |
|---|---|
| % of subjects with anti-D ≥0.1 IU/mL | 10% |
| % of subjects with anti-T ≥0.1 IU/mL | 10% |
| % of subjects with anti-PT vaccine response | 10% |
| % of subjects with anti-FHA vaccine response | 10% |
| % of subjects with anti-PRN vaccine response | 10% |
| % of subjects with anti-HBs ≥10 mIU/mL | 10% |
| % of subjects with anti-Polio 1 ≥8 | 10% |
| % of subjects with anti-Polio 2 ≥8 | 10% |
| % of subjects with anti-Polio 3 ≥8 | 10% |
| **Geometric Mean Titers (GMT)** | **Max ratio** |
| Anti-PT GMT | 1.5 |
| Anti-FHA GMT | 1.5 |
| Anti-PRN GMT | 1.5 |
| Anti-HBs GMT* | 2.0 |

*Secondary endpoint

According to the study objectives, non-inferiority was demonstrated when, for all study primary endpoints, the upper limit of the 90% CI for the difference (in the case of seroprotection/vaccine response rates) and ratio (in the case of GMTs) between groups was below the specified clinical limit of non-inferiority (one-sided equivalence test; alpha = 5%). See Figure 1 which graphically illustrates the approach to non-inferiority testing. Likewise, consistency was demonstrated when, for all study primary endpoints, and for all pair-wise comparisons of vaccines (lots), the 90% CI for the difference and ratio between vaccines (lots) was included in the specified clinical limits of equivalence (two-sided equivalence test; alpha = 5%).

**Figure 1: Approach to Analysis of Non-Inferiority**




For the differences in seroprotection and vaccine response rates, exact 90% CIs were calculated using "StatXact 3.0". For GMT ratios, the 90% CIs were derived from a one-way ANOVA model on the logarithm of the titers, assuming that the logarithm of the titers were normally distributed and had a common variance across groups.

### *2.2.2.4 Comparison with separately-administered US-licensed control vaccines (DTPa, HepB, OPV and IPV)*

The immunogenicity of the combined SBB DTPa-HepB-IPV vaccine administered concomitantly at separate sites with a U.S.-licensed Hib vaccine according to a 2, 4, 6 month schedule as compared with separate administration of US-licensed vaccines according to the same schedule was evaluated in an open, randomized study conducted in healthy infants in the USA (study DTPa-HepB-IPV-015).

***Objective***

A total of 400 healthy infants were enrolled and randomized (1:1:1:1) to one of four groups as follows:

Group 1: SBB DTPa-HepB-IPV + AP Hib vaccine administered separately at 2, 4 and 6 months of age

Group 2: SBB DTPa-HepB-IPV + AP Hib vaccine administered separately at 2 and 4 months of age with SBB DTPa-HepB + AP Hib + Lederle OPV separately at 6 months of age

Group 3: SBB DTPa-HepB + AP Hib + AP IPV administered separately at 2, 4 and 6 months of age

Group 4: SBB DTPa + SBB HepB + AP Hib + Lederle OPV administered separately at 2, 4 and 6 months of age

Of the 400 subjects enrolled in the study (100 in each of the four groups), 332 (91 in Group 1, 82 in Group 2, 81 in Group 3, and 78 in Group 4) were eligible for the ATP analysis of immunogenicity.

The primary objective of the study was to show non-inferiority of 3 doses of the combined SBB DTPa-HepB-IPV vaccine (group1) as compared to group 4 (U.S.-licensed individual vaccines) with respect to the criteria described in section 2.2.2.3 and non-inferiority to group 2 and 3 with respect to polio seroprotection rates.

***Results***

- One month after completion of the primary vaccination series, more than 98% of subjects in each group had anti-D and anti-T antibody titers ≥0.1 IU/ml, and anti-HBs antibody titers ≥10 mIU/ml [Figure 2 – shows data for group 1 and group 4 ( 3 doses of combined versus separate)].

- Similarly, the observed vaccine response rates to each pertussis antigen were high (91–100%) in all four groups (Figure 2; groups 1 and 4)).

- In addition, more than 98% of subjects had detectable neutralizing activity (titer ≥8) to each of the polio antigens, with the lower boundary of the 95% confidence interval on the point estimate exceeding 92% in all four groups (Figure 2; groups 1 and 4).

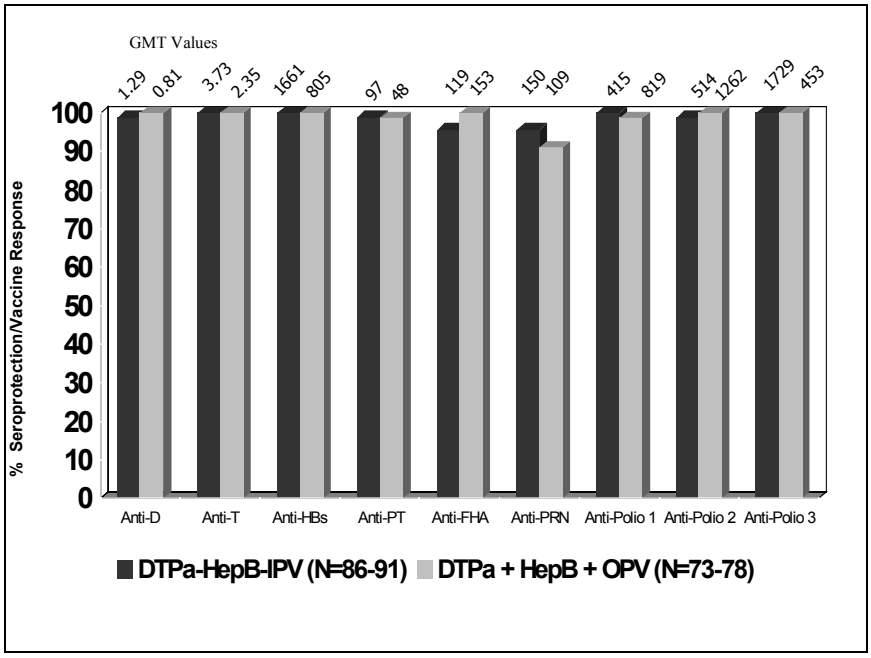
- Three doses of the combined SBB DTPa-HepB-IPV vaccine were at least as immunogenic as three doses of US-licensed separately-administered vaccines, in terms of seroprotection/ vaccine response rates, for all antigens other than FHA: the upper limit of the 90% CI of the vaccine group difference was below the *a priori* specified clinical limit for non-inferiority (10%) (Figure 3).

- In addition, the combined SBB DTPa-HepB-IPV vaccine was at least as immunogenic as US-licensed separately-administered vaccines in terms of post-vaccination GMTs for anti-PT, anti-FHA, and anti-PRN: for all antigens, including FHA, the upper limit of the 90% CI of the treatment ratio was below the *a priori* specified clinical limit for non-inferiority (1.5 for pertussis antigens), although for FHA the upper limit approached this pre-specified limit (Figure 3). SBB DTPa-HepB-IPV vaccine was also at least as immunogenic as U.S.-licensed separately administered vaccines in terms of post-vaccination GMTs for anti-HBs: the upper limit of the 90% confidence interval of the treatment ratio (0.7) was below the *a priori* specified clinical limit for non-inferiority (2.0 for anti-HBs).

- Furthermore, the combined SBB DTPa-HepB-IPV vaccine was at least as immunogenic in terms of seroprotection rates for each of the polio antigens as separately-administered US-licensed IPV vaccine (Group 3; Figure 5); the upper limit of the 90% CI of the vaccine group differences was below the clinical limit for non-inferiority (10%) for all three polio serotypes (Figure 6).

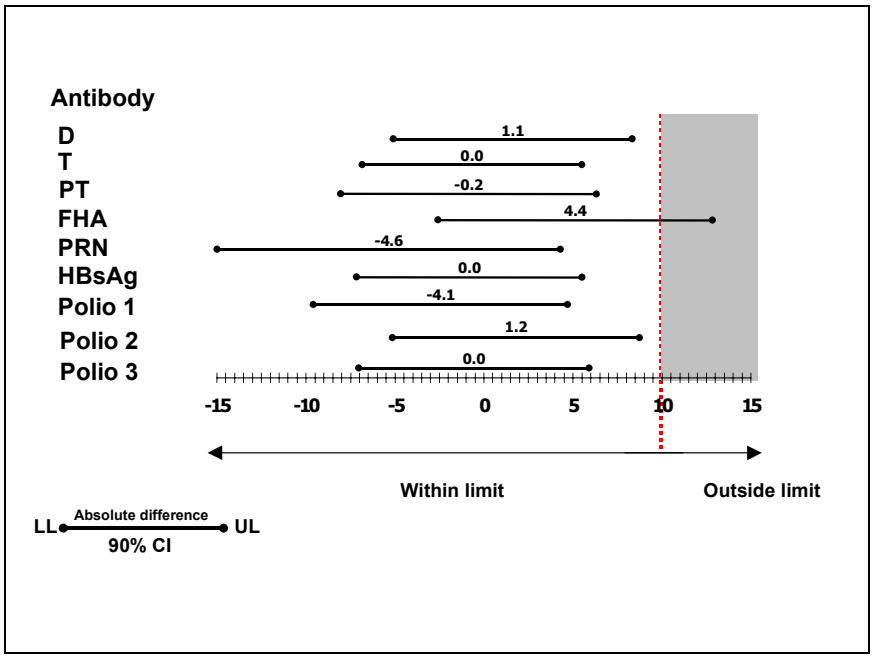
Reverse cumulative curves showing distribution of titers by antigen for groups 1 and 4 (for D, T, HBs, PT, FHA, PRN and PRP) and for groups 1, 3, and 4 (for polio) in study DTPa-HepB-IPV-015 can be found in Appendix IV (Figures 20 through 29). Results for anti-PRP antibody titers from study DTPa-HepB-IPV-015 are discussed in section 2.2.2.7.

**Figure 2: Immunogenicity of the SBB DTPa-HepB-IPV vaccine and U.S.-licensed vaccines administered separately (Group 1 vs. Group 4) - Study DTPa-HepB-IPV-015**




Group 1 – SBB DTPa-HepB-IPV x 3 (at 2, 4 and 6 months of age)
Group 4 – SBB DTPa + SBB HepB + Lederle OPV x 3 (at 2, 4 and 6 months of age)
% = Percentage of subjects with SP/VR
GMT – Geometric Mean Titers
**Seroprotection definition:**
•Diphtheria, tetanus antibodies: subjects with post-vaccination titers ≥0.1 IU/mL
•HBsAg antibodies: subjects with post-vaccination titers ≥10 mIU/mL
•Polio antibodies: subjects with post-vaccination titers ≥8
**Vaccine Response definition:**
•Pertussis antibodies:
–initially seronegative subjects with post-vaccination titer ≥ cut-off (5 EL.U/mL)
–initially seropositive subjects with post-vaccination titer ≥ pre-vaccination titer

**Figure 3: Non-inferiority testing of Seroprotection/Vaccine Response % for all antibodies (Group 4 minus Group 1) - Study DTPa-HepB-IPV-015**




Group 1 – SBB DTPa-HepB-IPV x 3 (at 2, 4 and 6 months of age)
Group 4 – SBB DTPa + SBB HepB + Lederle OPV x 3 (at 2, 4 and 6 months of age)
Value above the bar is the point estimate of the absolute difference of seroprotection/vaccine response % (Group 4 minus Group 1)
90% CI = 90% confidence interval; LL = Lower limit, UL = Upper limit

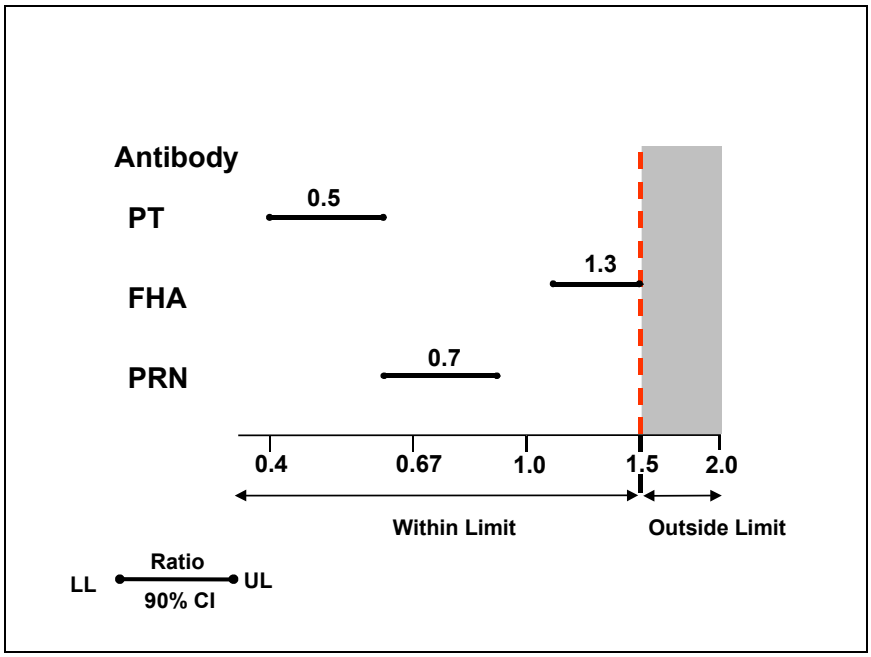
**Seroprotection definition:**

•Diphtheria, tetanus antibodies: subjects with post-vaccination titers ≥0.1 IU/mL
•HBs antibodies: subjects with post-vaccination titers ≥10 mIU/mL
•Polio antibodies: subjects with post-vaccination titers ≥8

**Vaccine Response definition:**

•Pertussis antibodies:
–initially seronegative subjects with post-vaccination titer ≥ cut-off (5 EL.U/mL)
–initially seropositive subjects with post-vaccination titer ≥ pre-vaccination titer

**Figure 4: Non-inferiority testing of Ratio of Pertussis GMTs for anti-PT, anti-FHA and anti-PRN (Group 4 divided by Group 1) - Study DTPa-HepB-IPV-015**

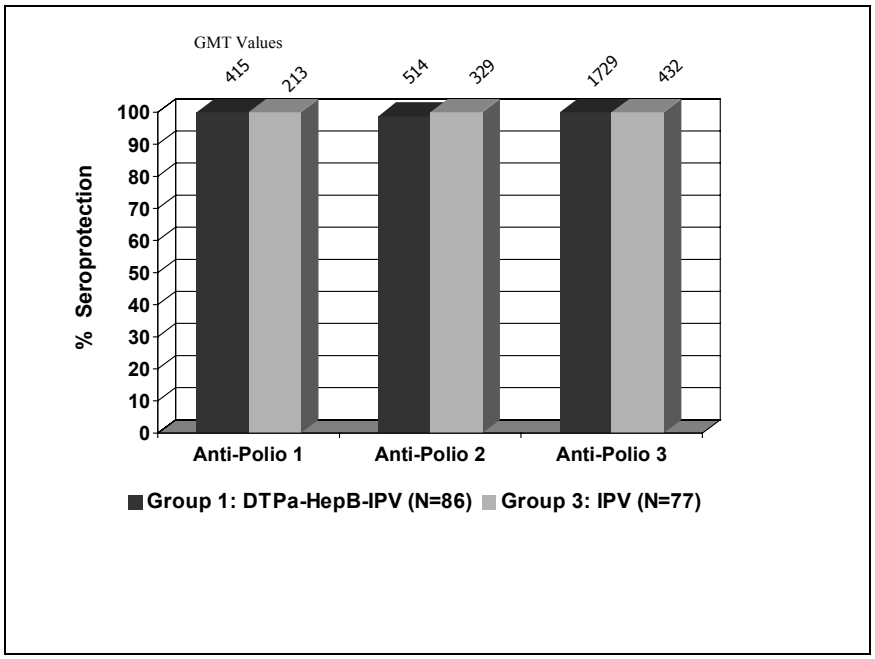



Group 1 – SBB DTPa-HepB-IPV x 3 (at 2, 4 and 6 months of age)
Group 4 – SBB DTPa + SBB HepB + Lederle OPV x 3 (at 2, 4 and 6 months of age)

Value above the bar is the point estimate of the ratio of GMTs (Group 4 divided by Group 1)

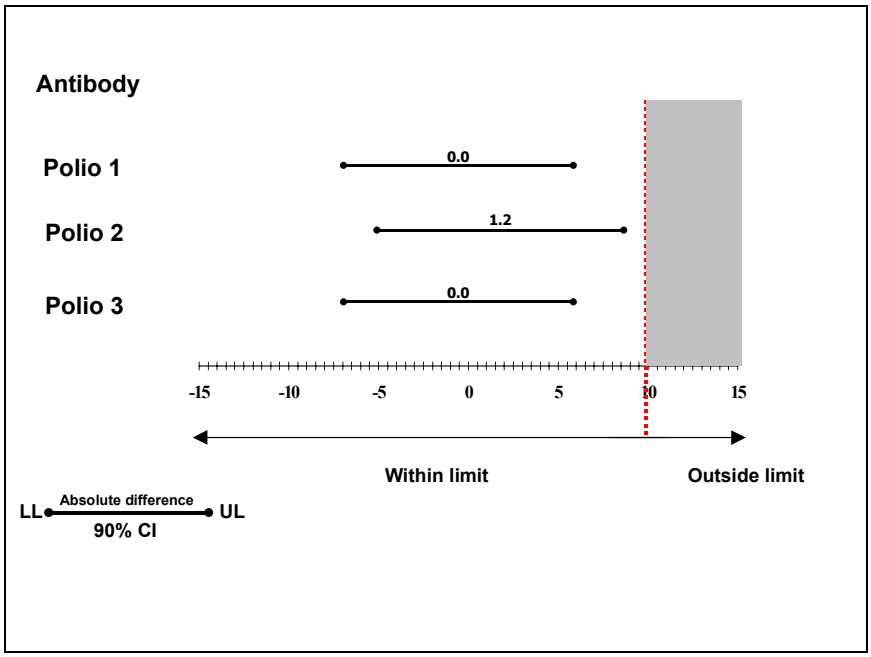
90% CI = 90% confidence interval; LL = Lower limit, UL = Upper limit

**Figure 5: Immune responses to the polio antigens following administration of three doses of SBB DTPa-HepB-IPV vaccine as compared with three doses of US-licensed IPV vaccine administered separately (Group 1 vs. Group 3) - Study DTPa-HepB-IPV-015**




Group 1 – SBB DTPa-HepB-IPV x 3 (at 2, 4 and 6 months of age)
Group 3 – SBB DTPa-HepB + AP IPV x 3 (at 2, 4, and 6 months of age)
% = Percentage of subjects with SP
**Seroprotection definition:** subjects with post-vaccination polio antibody titers ≥8

**Figure 6: Non-inferiority testing of Seroprotection % for anti-polio (Group 3 minus Group 1) - Study DTPa-HepB-IPV-015**




Group 1 – SBB DTPa-HepB-IPV x 3 (at 2, 4 and 6 months of age)
Group 3 – SBB DTPa-HepB + AP IPV x 3 (at 2, 4 and 6 months of age)
% = Percentage of subjects with SP
Value above the bar is the point estimate of the absolute difference (Group 3 minus Group 1)
90% CI = 90% confidence interval; LL = Lower limit, UL = Upper limit
**Seroprotection definition**: subjects with post-vaccination polio antibody titers ≥8

***Conclusions***

When administered according to a three-dose primary vaccination schedule at 2, 4 and 6 months of age, the SBB DTPa-HepB-IPV vaccine provides protection against diphtheria, tetanus, hepatitis B and polio. The vaccine will provide protection to an equivalent degree as US-licensed vaccines administered separately at 2, 4 and 6 months of age. In addition, the vaccine will provide an equivalent degree of protection against polio as three doses of separately-administered US-licensed IPV vaccine.

In this study, anti-pertussis (PT, FHA and PRN) antibody titers following administration of the SBB DTPa-HepB-IPV vaccine were similar to those following administration of the SBB *Infanrix* (DTPa). Furthermore, the vaccine responses to the PT and PRN antigens were equivalent. The observed vaccine response to the FHA antigen following administration of the SBB DTPa-HepB-IPV vaccine was somewhat lower than the response following administration of *Infanrix* (the upper limit of the 90% CI for vaccination difference marginally exceeded the pre-defined limit of non-inferiority). This could be a consequence of the known biological variability in the response to the pertussis antigens (in particular the response to FHA). In addition, it has recently been suggested that, in the presence of antibody to PT and PRN, the additional presence of antibody to FHA is of limited contribution to protection [1,2]. Importantly, when plotted on reverse cumulative distribution curves (RCCs), the antibody titers observed one month after completion of the primary series in study 015, were similar to those observed following a three dose primary series of Infanrix® in two efficacy studies (NIH sponsored Italian trial [10]; SBB sponsored German Household Contact Study[9]. Therefore, it can be concluded that the SBB DTPa-HepB-IPV vaccine also will be efficacious against pertussis.

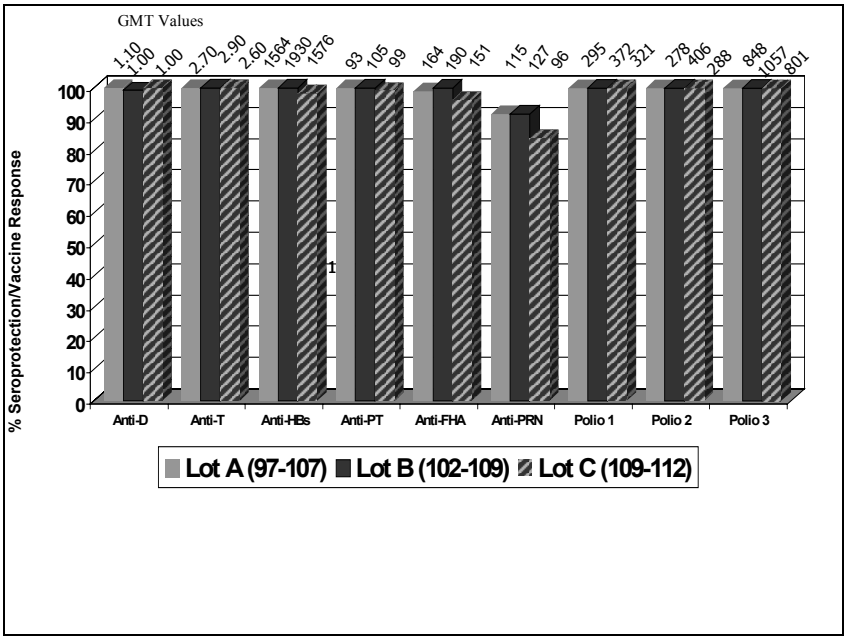
This study demonstrated that the DTPa-HepB-IPV vaccine is comparably immunogenic to US-licensed DTPa, HepB, OPV and IPV vaccines administered separately and simultaneously.

#### *2.2.2.5 Lot-to-lot consistency*

Clinical consistency of three lots each of the First and Second Lot Series of the SBB DTPa-HepB-IPV vaccine was assessed in two separate double-blind, randomized clinical studies in Europe (DTPa-HepB-IPV-005, N enrolled ≅ 160 per group) and the USA (DTPa-HepB-IPV-044, N enrolled ≅ 120 per group), respectively. The First Lot Series of the SBB DTPa-HepB-IPV vaccine (study DTPa-HepB-IPV-005) was shown to be statistically consistent with regard to all antigens contained in the vaccine (data not shown). The Second Lot Series of the SBB DTPa-HepB-IPV vaccine was shown to be statistically consistent for D, T, PT, HepB, and polio types 1, 2, and 3 (Figures 7, 8 & 9). However, the limits of the 90% CIs of the differences in vaccine response rates between the lots were exceeded for vaccine response rates to FHA and PRN (Figure 10). The three vaccine lots were consistent in terms of post-vaccination GMTs for anti-PT and anti-FHA: the limits of the 90% CI of the ratio were within the pre-specified limits of equivalence (0.67, 1.5). For anti-PRN, the 90% CI on the ratio of GMTs for one lot comparison (0.63) marginally exceeded the pre-specified limit (Figure 11). These differences were not as apparent when the data was re-analyzed, taking into account the impact of maternal antibody, as discussed in the text that follows the aforementioned figures.

It is important to note that, the same three DTPa-HepB-IPV lots (as used in study DTPa-HepB-IPV-044) were mixed extemporaneously prior to administration in two additional studies (DTPa-HepB-IPV/Hib-027 and DTPa-HepB-IPV/Hib-048). Equivalence testing for the percent seroprotection/vaccine response and GMTs for all antigens is presented in Appendix V as Figures 30, 31, 32 and 33.

**Figure 7: Immunogenicity of three lots (the Second Lot Series) of the SBB DTPa-HepB-IPV vaccine - Study DTPa-HepB-IPV-044**




% = Percent of subjects with SP/VR
GMT = Geometric Mean Titer

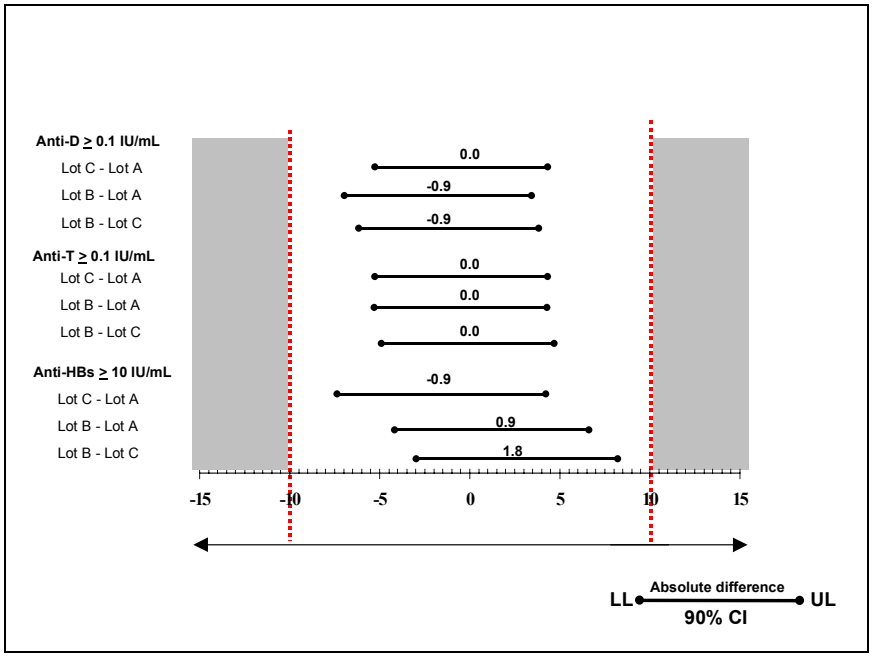
**Seroprotection definition:**

•Diphtheria, tetanus antibodies: subjects with post-vaccination titers ≥0.1 IU/mL
•HBsAg antibodies: subjects with post-vaccination titers ≥10 mIU/mL
•Polio antibodies: subjects with post-vaccination titers ≥8

**Vaccine Response definition:**

•Pertussis antibodies:
– initially seronegative subjects with post-vaccination titer ≥ cut-off (5 EL.U/mL)
– initially seropositive subjects with post-vaccination titer ≥ pre-vaccination titer

**Figure 8: Equivalence testing of Seroprotection % for anti-D, anti-T, and anti-HBs (Lot-to-Lot consistency) - Study DTPa-HepB-IPV-044**




Value above the bar is the point estimate of the absolute difference of seroprotection %

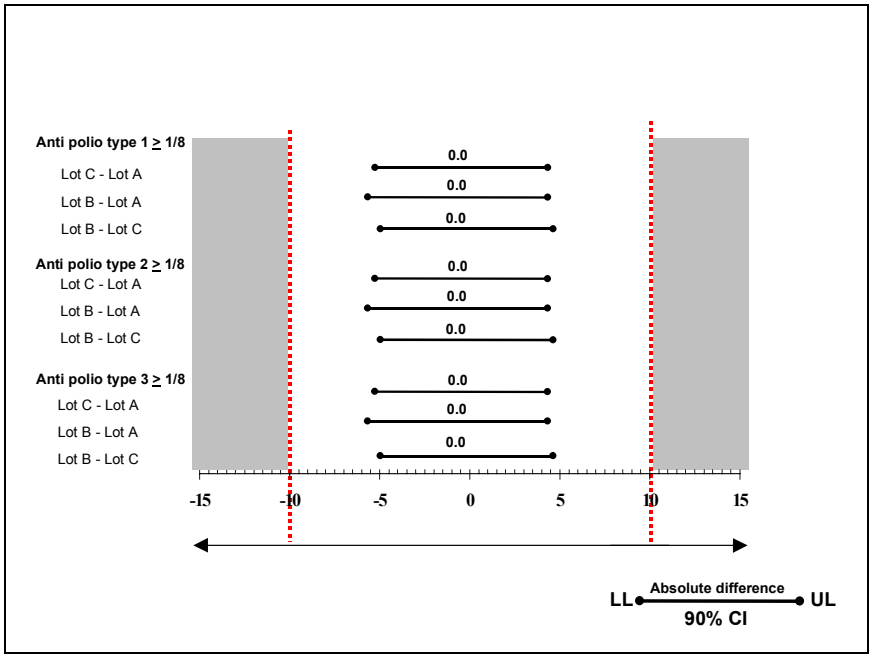
90% CI = 90% confidence interval; LL = Lower limit; UL = Upper limit

**Seroprotection definition:**

Diphtheria, tetanus antibodies: subjects with post-vaccination titers ≥0.1 IU/mL

HBs antibodies: subjects with post-vaccination titers ≥10 mIU/mL

**Figure 9: Equivalence Testing of Seroprotection % for anti-polio 1, 2 and 3 (Lot-to-Lot consistency) - Study DTPa-HepB-IPV-044**

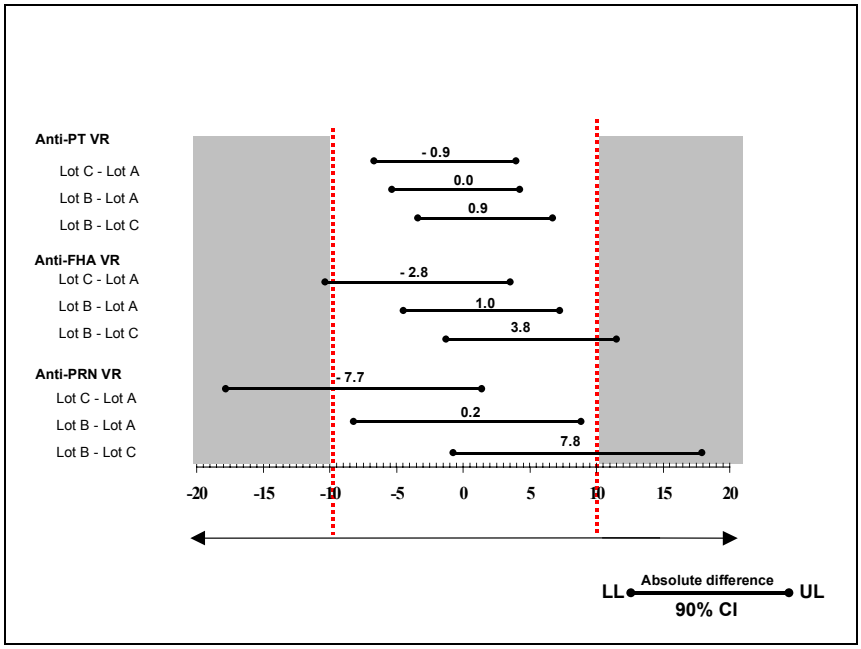



Value above the bar is the point estimate of the absolute difference of seroprotection %
90% CI = 90% confidence interval; LL = Lower limit; UL = Upper limit

**Seroprotection definition:**

•Polio antibodies: subjects with post-vaccination titers ≥8

**Figure 10: Equivalence Testing of VR % for anti-PT, anti-FHA and anti-PRN (Lot-to-Lot consistency) - Study DTPa-HepB-IPV-044**




Value above the bar is the point estimate of the absolute difference of vaccine response %
90% CI = 90% confidence interval; LL = lower limit, UL = upper limit

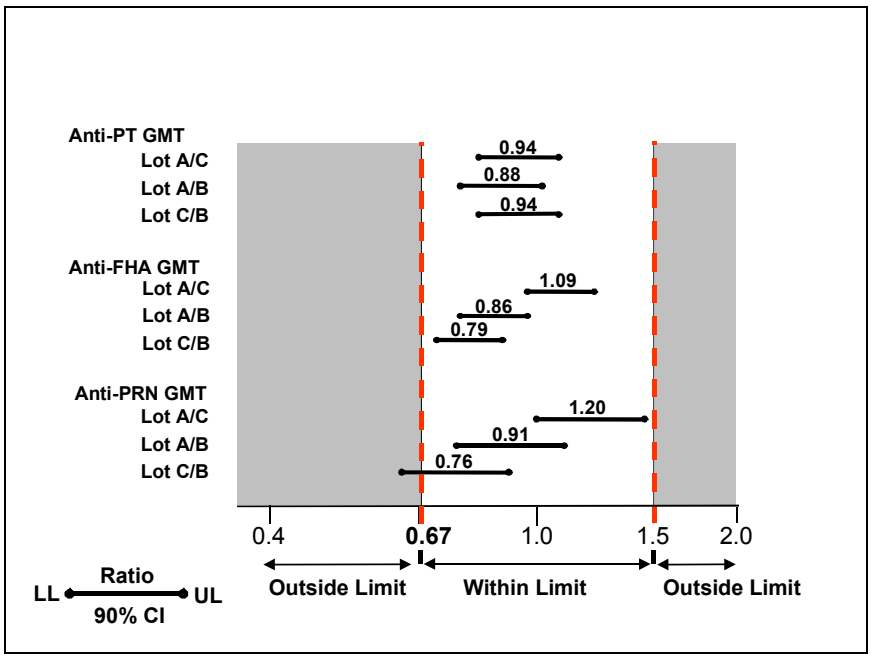
**Vaccine Response definition:**

•Pertussis antibodies:

– initially seronegative subjects with post-vaccination titer ≥ cut-off (5 EL.U/mL)

– initially seropositive subjects with post-vaccination titer ≥ pre-vaccination titer

**Figure 11: Equivalence Testing of GMTs for anti-PT, anti-FHA and anti-PRN (Lot-to-Lot consistency) - Study DTPa-HepB-IPV-044**



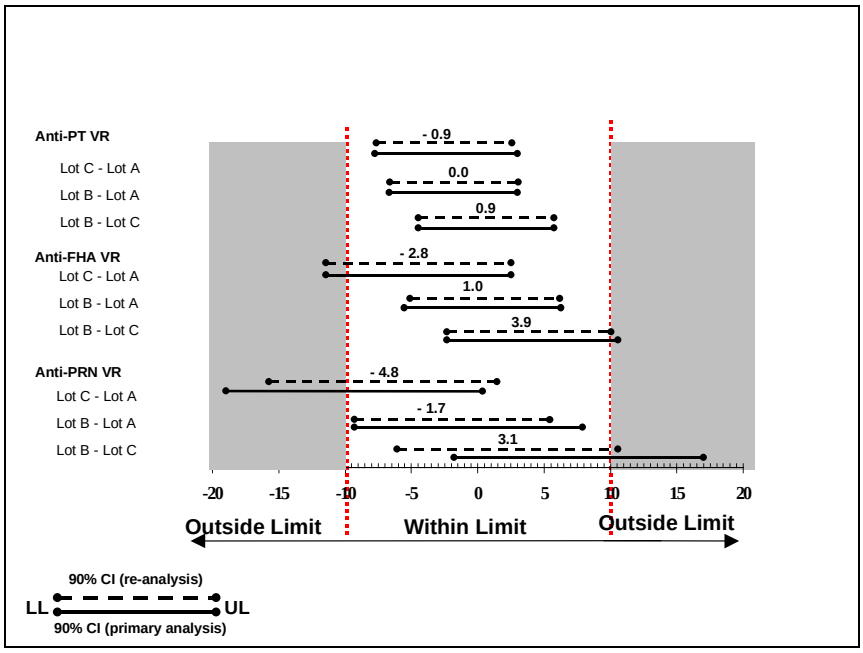

Value above the bar is the point estimate of the ratio of GMTs
90% CI = 90% confidence interval; LL = lower limit, UL = upper limit

A possible explanation for the lot differences observed in study 044 are related to an imbalance between groups in the number of subjects with high maternal antibody levels prior to vaccination which could not be controlled for *a priori.* It has been reported previously that infants with high levels of maternal antibody are more likely to have a lower antibody titer post-vaccination and are less likely to achieve a vaccine response as defined in the protocol (3, 4). Such a negative correlation between post-vaccination and pre-vaccination titer was observed in this study as demonstrated by linear regression analysis of the post/pre ratio as a function of pre-vaccination titer (data not shown).

An analysis of the vaccine response after exclusion of subjects with high pre-vaccination antibody titer (selected on the basis of the linear regression analysis) was also performed. Although this analysis is not satisfactory as it results in power loss (small N) and it does not account for possible imbalance in lower pre-

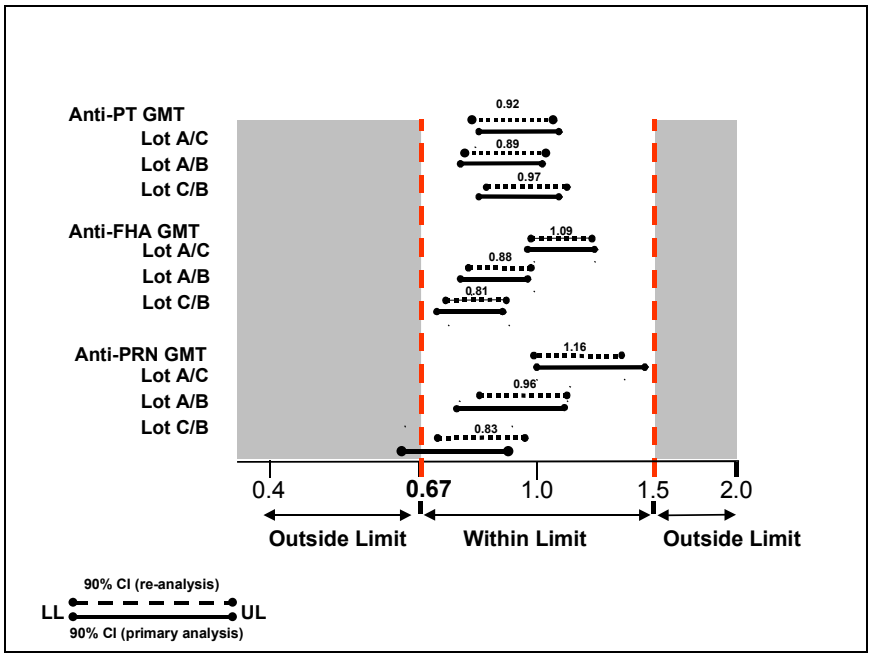
vaccination titers, it showed that the differences in vaccine response rates between groups were reduced as compared to the analysis including all subjects. Figure 12 shows the data from both the primary analysis (solid line) and data following re-analysis (dotted line) after exclusion of subjects with high pre-vaccination antibody titers. An analysis of covariance (ANCOVA) of the post-vaccination antibody titer as a factor of both vaccine lot and pre-vaccination titer showed that, when the pre-vaccination titer was taken into account, the three lots were equivalent in terms of post-vaccination GMTs. Figure 13 shows the data from both the primary analysis (solid line) and data following re-analysis (dotted line) after adjustment for subjects with high pre-vaccination antibody titers.

**Figure 12: Re-analysis of the consistency of the Second Lot Series of the SBB DTPa-HepB-IPV vaccine in terms of immune response to the pertussis antigens after adjustment for pre-vaccination titer: vaccine response calculated after elimination of subjects with high*pre-vaccination titers (Study DTPa-HepB-IPV-044)**




Value above the bar is the point estimate of the absolute difference of vaccine response % for the re-analysis
90% CI = 90% confidence interval; LL = Lower limit, UL = Upper limit
**Vaccine Response definition:**
•Pertussis antibodies:
– initially seronegative subjects with post-vaccination titer ≥ cut-off (5 EL.U/mL)
– initially seropositive subjects with post-vaccination titer ≥ pre-vaccination titer
* Anti-PT titer ≥54 EL.U/ml; Anti-FHA titer ≥119 EL.U/ml; Anti-PRN titer ≥56 EL.U/ml

**Figure 13: Re-analysis of the consistency of the Second Lot Series of the SBB DTPa-HepB-IPV vaccine in terms of immune response to the pertussis antigens : GMT analyzed after adjustment for pre-vaccination titer (ANCOVA) - Study DTPa-HepB-IPV-044**




Value above the bar is the point estimate of the ratio of GMTs
90% CI = 90% confidence interval; LL = lower limit, UL = upper limit

The same Second Lot Series lots were employed in two other studies in which the vaccine was used to reconstitute lyophilized Hib vaccine (manufactured by SB Biologicals). One of these studies was conducted in the US (Protocol DTPa-HepB-IPV/Hib-027), with the vaccine being administered on a 2, 4, 6 month schedule and the second study was conducted in Germany (Protocol DTPa-HepB-IPV/Hib-048), with the vaccine administered on a 3, 4, 5 month schedule. It is important to note that in both studies, consistency was demonstrated for all three pertussis antigens using the equivalence approach with the same pre-specified criteria as in DTPa-HepB-IPV-044 (consistency & bridging). Equivalence testing for anti-pertussis antibodies from these two studies can be found in Appendix V.

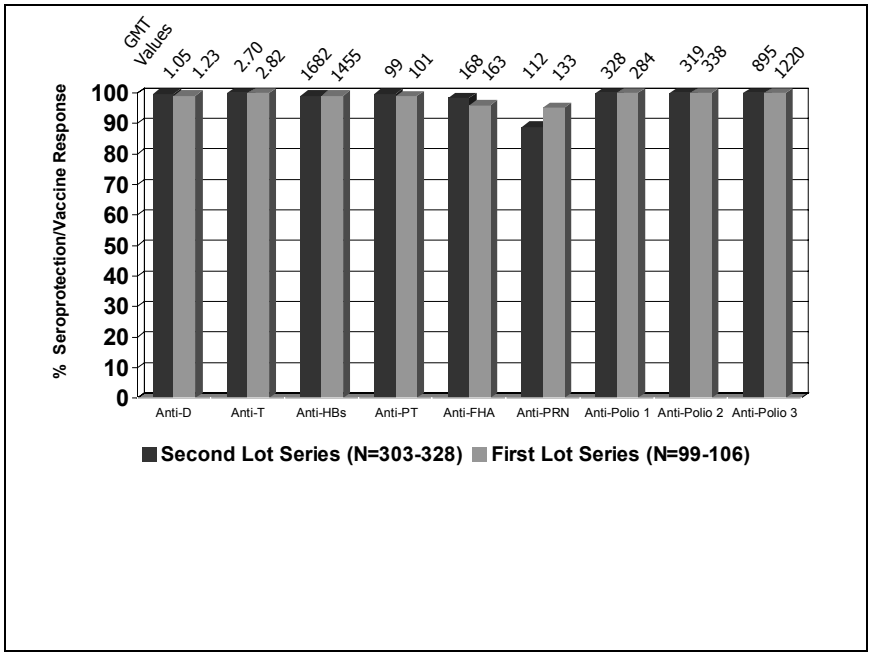
***Conclusion***

These studies demonstrate that the immune response elicited to each antigen of the DTPa-HepB-IPV vaccine is consistent across different lots of vaccine.

### *2.2.2.6 Comparison of the First Lot Series to the Second Lot Series*

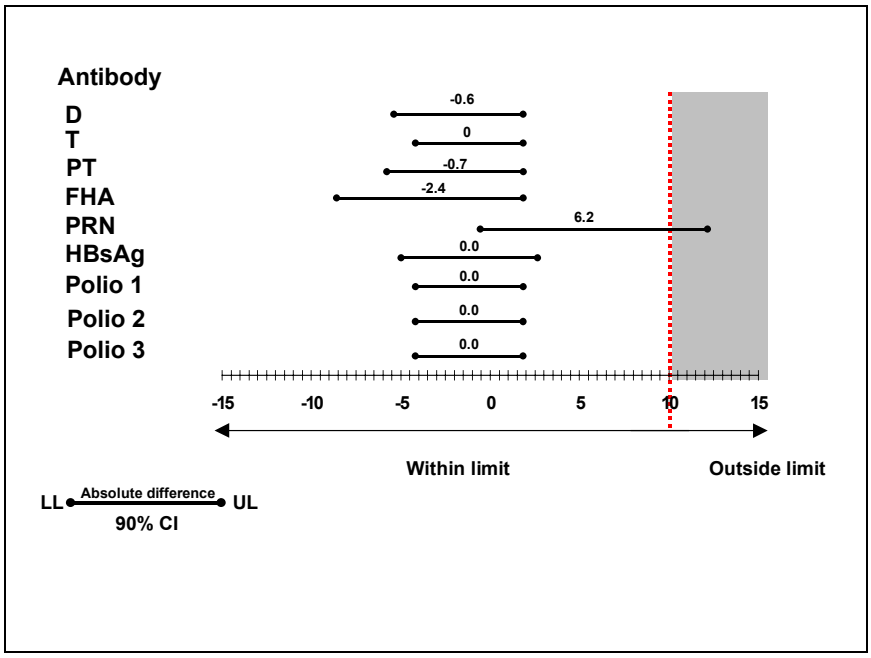
Study DTPa-HepB-IPV-044 also evaluated the immunogenicity of the Second Lot Series (N enrolled = 363) as compared with the First Lot Series (N enrolled = 121) in a double blind randomized fashion. The Second Lot Series was shown to be at least as immunogenic as the First Lot Series in terms of all parameters of primary interest other than the rate of vaccine response to PRN (see Figures 14, 15, & 16). After adjustment for high pre-vaccination antibody titers to the pertussis antigens (as was performed for the analysis of consistency), the Second Lot Series was shown to be at least as immunogenic as the First Lot Series for all parameters of primary interest as shown in Figures 17 and 18 (specific to pertussis antigens). As before, data following the primary analysis is shown using a solid line and after adjustment for pre-vaccination titer using a dotted line.

**Figure 14: Immunogenicity of First and Second Lot Series of the SBB DTPa-HepB-IPV vaccine - Study DTPa-HepB-IPV-044**




% = Percentage of subjects with SP/VR
GMT = Geometric Mean Titer
**Seroprotection definition:**
•Diphtheria, tetanus antibodies: subjects with post-vaccination titers ≥0.1 IU/ml
•HBs antibodies: subjects with post-vaccination titers ≥10 mIU/ml
•Polio antibodies: subjects with post-vaccination titers ≥8
**Vaccine Response definition:**
•Pertussis antibodies:
– initially seronegative subjects with post-vaccination titer ≥ cut-off (5 EL.U/ml)
– initially seropositive subjects with post-vaccination titer ≥ pre-vaccination titer
Second Lot Series = pooled data from lots A, B, & C

**Figure 15: Non-inferiority testing of Seroprotection/Vaccine Response % (First minus Second Lot series) - Study DTPa-HepB-IPV-044**




Value above the bar is the point estimate of the absolute difference of seroprotection/vaccine response % (First minus Second Lot series)

90% CI = 90% confidence interval; LL = Lower limit; UL = Upper limit

**Seroprotection definition:**

•Diphtheria, tetanus antibodies: subjects with post-vaccination titers ≥0.1 IU/ml

•HBs antibodies: subjects with post-vaccination titers ≥10 mIU/ml

•Polio antibodies: subjects with post-vaccination titers ≥8

**Vaccine Response definition:**

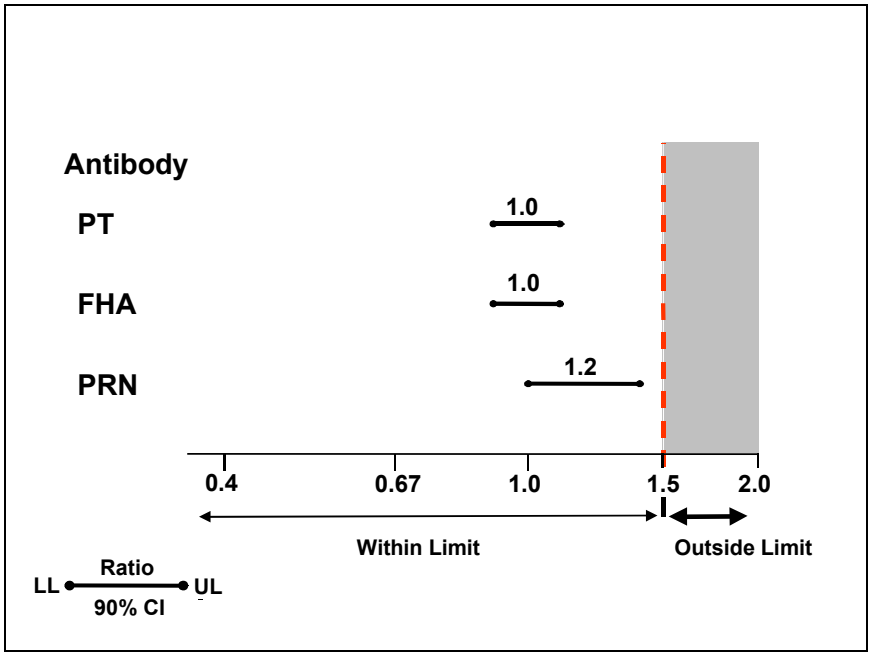
•Pertussis antibodies:

– initially seronegative subjects with post-vaccination titer ≥ cut-off (5 EL.U/ml)

– initially seropositive subjects with post-vaccination titer ≥ pre-vaccination titer

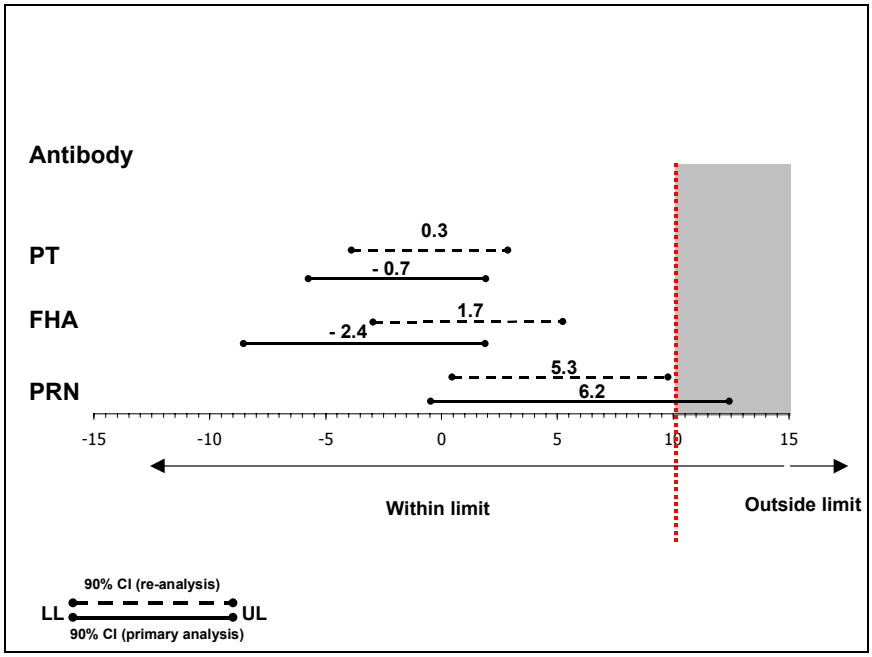
Second Lot Series = pooled data from lots A, B, & C

**Figure 16: Non-inferiority testing of Ratio of GMT for anti-PT, anti-FHA, and anti-PRN (First divided by Second lot series) - Study DTPa-HepB-IPV-044**



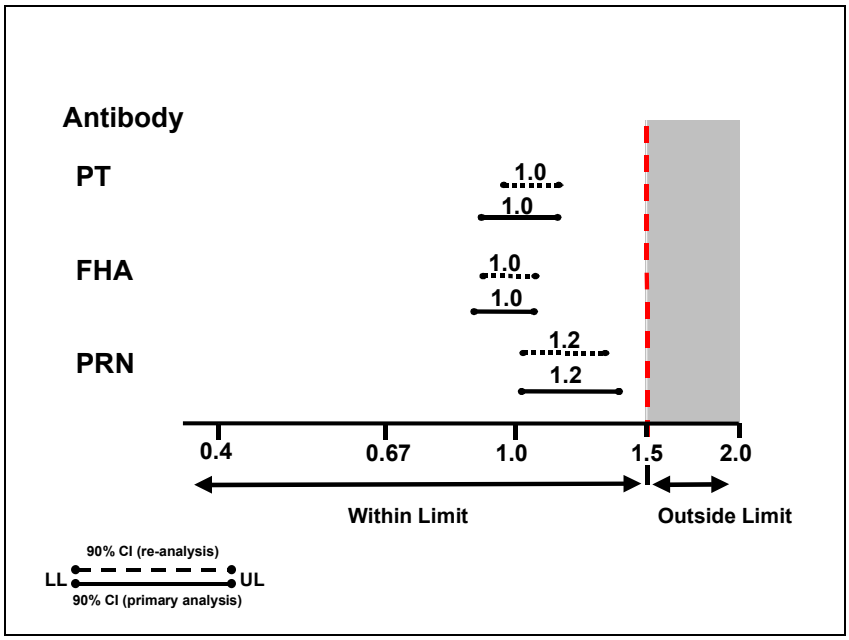

Value above the bar is the point estimate of the ratio of GMTs (First divided by Second Lot series)
90% CI = 90% confidence interval; LL = Lower limit; UL = Upper Limit
Second Lot Series = pooled data from lots A, B, & C

**Figure 17: Re-analysis of the comparison of the immunogenicity of the First and Second Lot Series of the SBB DTPa-HepB-IPV vaccine in terms of immune response to the pertussis antigens after adjustment for pre-vaccination titer: vaccine response calculated after elimination of subjects with high*pre-vaccination titers (Study DTPa-HepB-IPV-044)**




Value above the bar is the point estimate of the absolute difference of vaccine response % (First minus Second Lot series)
90% CI = 90% confidence interval; LL = Lower limit, UL = Upper limit
**Vaccine Response definition:**
•Pertussis antibodies:
– initially seronegative subjects with post-vaccination titer ≥ cut-off (5 EL.U/mL)
– initially seropositive subjects with post-vaccination titer ≥ pre-vaccination titer
* Anti-PT titer ≥54 EL.U/ml; Anti-FHA titer ≥119 EL.U/ml; Anti-PRN titer ≥56 EL.U/ml
Second Lot Series = pooled data from lost A, B & C

**Figure 18: Re-analysis of the comparison of the immunogenicity of the First and Second Lot Series of the SBB DTPa-HepB-IPV vaccine in terms of immune response to the pertussis antigens: GMT analyzed after adjustment for pre-vaccination titer (ANCOVA) - Study DTPa-HepB-IPV-044**




Value above the bar is the point estimate of the ratio of GMTs (First Lot divided by Second Lot series)
90% CI = 90% confidence interval; LL = Lower limit, UL = Upper limit

***Conclusion***

This study demonstrates that the manufacturing change made between the vaccine lot employed in earlier clinical studies (First Lot series) and the Second Lot Series has no impact on the immunological response of the vaccine.

### *2.2.2.7 Effect of co-administration with licensed Hib vaccines*

Examination of data from two open, randomized studies, one in Lithuania (DTPa-HepB-IPV-012; N enrolled = 549) and one in the USA (DTPa-HepB-IPV-015), in which licensed Hib vaccine was administered concomitantly at separate sites with the SBB DTPa-HepB-IPV candidate vaccine, showed that the SBB DTPa-HepB-IPV vaccine and licensed Hib vaccines are highly immunogenic for all antigens when co-administered concomitantly at separate sites. Note that in study DTPa-HepB-IPV-012, several US-licensed Hib vaccines were employed including, AP's PRP-T, Lederle's HbOC and Merck's PRP-OMP. The majority (≥98%) of subjects had protective titers against diphtheria, tetanus and HepB after vaccination as well as neutralizing antibody to each of the three polio antigens, most (91–100%) had a vaccine response to each of the pertussis antigens, and at least 98% of subjects in each group had anti-PRP titers ≥0.15 mcg/mL (Table 6). Data for the other antigens is included and discussed in section 2.2.2.4.

**Table 6: Immunogenicity of Hib vaccine following simultaneous administration at separate sites with SBB DTPa-HepB-IPV (Studies DTPa-HepB-IPV-012 & DTPa-HepB-IPV-015)**

| Study | Group | N | % ≥0.15 mcg/ml | | % ≥1.0 mcg/ml | | GMC (mcg/ml) | |
|---|---|---|---|---|---|---|---|---|
| (schedule) | | | | [95 % CI] | | [95 % CI] | | [95 % CI] |
| DTPa-HepB-IPV-012 | Group 1 | 202 | 100 | [97.7–100] | 96.0 | [92.1–98.1] | 7.2 | [6.2–8.3] |
| (3, 4.5, 6 m) | Group 2 | 101 | 99.0 | [93.8–99.9] | 94.1 | [87.0–97.6] | 6.7 | [5.4–8.2] |
| | Group 3 | 100 | 100 | [95.4–100] | 88.0 | [79.6–93.4] | 5.8 | [4.4–7.5] |
| | Group 4 | 105 | 100 | [95.6–100] | 90.5 | [82.8–95.1] | 5.0 | [4.0–6.1] |
| DTPa-HepB-IPV-015 | Group 1 | 90 | 98.9 | [94.0–100] | 94.4 | [87.5–98.2] | 6.2 | [4.9–7.8] |
| (2, 4, 6 m) | Group 4 | 78 | 100 | [95.4–100] | 94.9 | [87.4–98.6] | 7.8 | [6.1–10.1] |

Study DTPa-HepB-IPV-012:
Group 1 - SBB DTPa-HepB-IPV + SBB Hib
Group 2 - SBB DTPa-HepB-IPV + AP Hib
Group 3 - SBB DTPa-HepB-IPV + Lederle Hib
Group 4 - Dose 1 & 3: SBB DTPa-HepB-IPV + Merck Hib; Dose 2: SBB DTPa-HepB-IPV
Study DTPa-HepB-IPV-015:
Group 1 – SBB DTPa-HepB-IPV + AP Hib
Group 4 – SBB DTPa + SBB HepB + Lederle OPV + AP Hib
N = Number of subjects
% = Percentage of subjects 95% CI = 95% confidence interval

***Conclusion***

The DTPa-HepB-IPV vaccine can be coadministered with recommended Hib vaccine with no resultant impact on the immune response to any antigen of the DTPa-HepB-IPV or Hib vaccine.

NOTE: *Prevnar™* [Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM197)] was not routinely recommended for vaccination of infants, nor commercially available at the time of the submission of the BLA for DTPa-HepB-IPV. A study to evaluate the impact of co-administration of SB's DTPa-HepB-IPV with *Prevnar* will be conducted as a post-licensure commitment.

#### *2.2.2.8 Comparison of the immunogenicity of the HepB antigen when given in combination at 2, 4 and 6 months of age with that of US-licensed HepB vaccine when given at 0, 1, and 6 months of age*

The comparability of the response to the HepB component as part of a combination vaccine given at 2, 4, and 6 months of age to that of SBB HepB vaccine given according to a US-licensed regimen (0, 1, 6 months) was investigated in an open, randomized study conducted in the USA (DTPa-HepB-030). The composition of the DTPa-HepB vaccine used in this study was similar to the DTPa-HepB-IPV vaccine, except for the IPV component. Subjects received either SBB DTPa-HepB vaccine simultaneously at separate sites along with AP's Hib vaccine and Lederle OPV vaccine at 2, 4, and 6 months of age (N enrolled = 140) or SBB HepB vaccine at 0, 1, and 6 months of age (as well as separate injections of SBB DTPa vaccine and AP Hib vaccine and Lederle OPV vaccine at 2, 4, and 6 months of age; N enrolled = 140).

***Results***

- Post-vaccination, seroprotection rates were similarly high (>99%) in both groups. At 7 months of age, the proportion of subjects with anti-HBs ≥ 10 mIU/ml following administration of HepB antigen as part of the combination at 2, 4, and 6 months of age was not inferior to that following administration of SBB HepB vaccine (*Engerix-B*) according to the U.S.-licensed regimen (0, 1 and 6 months of age): the upper limit of the 90% confidence interval of the difference between groups was below the *a prior* specified limit for non-inferiority (10%, see Figure 19).

- The anti-HBs antibody GMT was lower when the HepB component was given on a 2, 4, 6 month schedule as part of the SBB DTPa-HepB combination (1052 mIU/mL vs. 3717 mIU/mL) (Table 7). This is likely due to the difference in schedule, as it has previously been reported that post-vaccination anti-HBs antibody GMTs are lower one month after HepB vaccination when the interval between doses is reduced. The clinical relevance is likely to be limited, given that virtually all subjects had protective titers (10 mIU/mL) post-vaccination; individuals with titers ≥10 mIU/mL should continue to be protected from both symptomatic and chronic HepB infection on the basis of immunologic memory, even in the absence of detectable antibody [5].

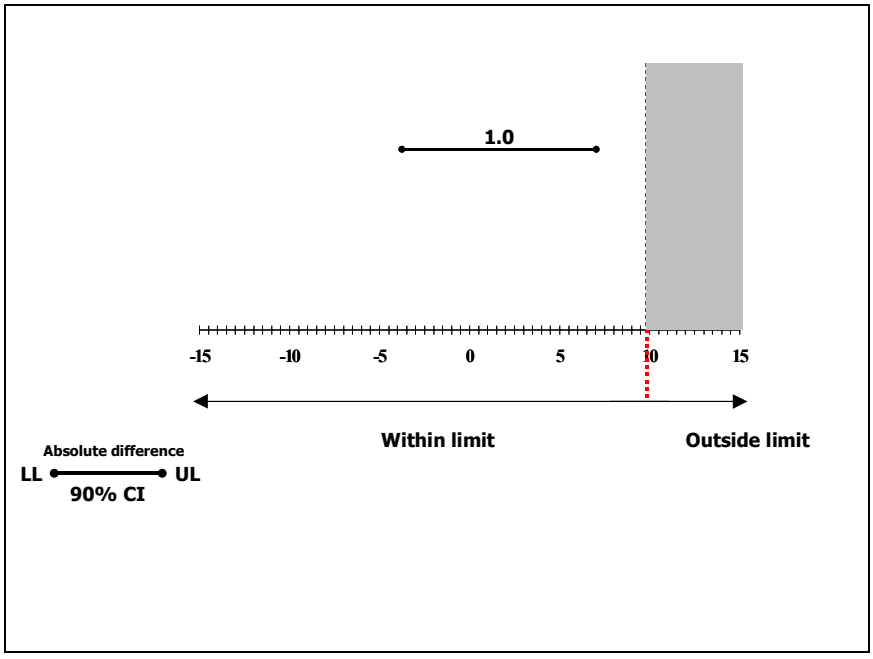
- Furthermore, the anti-HBs antibody GMT induced by SBB DTPa-HepB vaccination at 2, 4 and 6 months of age was in the range of GMTs previously reported following administration of licensed HepB vaccines shown to provide long-term protection from disease (Table 8).

**Table 7: Immunogenicity one month after a three-dose primary vaccination of the hepatitis B antigen administered either as a combined DTPa-HepB vaccine at 2, 4 and 6 months of age or as a US-licensed hepatitis B vaccine at 0, 1, 6 months of age (Study DTPa-HepB-030)**

| Antibody | Vaccine | N | SP* | | GMT (mIU/mL) | |
|---|---|---|---|---|---|---|
| | | | % | 95 % CI | | 95 % CI |
| HBs | DTPa-HepB (2, 4, 6 m) | 99 | 99.0 | [94.5–100] | 1052 | [804–1377] |
| | HepB (0, 1, 6 m) | 105 | 100 | [96.5–100] | 3717 | [2929–4718] |

N = Number of subjects with available results
% = Percentage of subjects with SP
95% CI = 95% confidence interval
*SP definition: subjects with post-vaccination titers ≥10 mIU/mL

**Figure 19: Non-inferiority testing of Seroprotection % for anti-HBs (HepB 0, 1, 6 minus DTPa-HepB 2, 4, 6) - Study DTPa-HepB-030**




Value above the bar is the point estimate of the absolute difference of seroprotection % (HepB 0,1, 6 minus DTPa-HepB 2, 4, 6)

90% CI = 90% Confidence interval; LL = Lower limit, UL = Upper limit

**Seroprotection definition**: subjects with post-vaccination titers ≥ 10 IU/mL

**Table 8: Immunogenicity of two US-licensed hepatitis B vaccines administered to neonates (0, 1, 6 Month Schedule)**

| Vaccine | HepB dose | N | Post-vaccination (Month 7–9) | | References |
|---|---|---|---|---|---|
| | | | % ≥ 10 mIU/mL | GMT (mIU/mL) | |
| SBB HepB* | 10 mcg | 103<br>52<br>50<br>23<br>41<br>38 | 96<br>97<br>98<br>100<br>93<br>100 | 248<br>713<br>1076<br>1168<br>1584<br>3211 | 12<br>13<br>14<br>15<br>16<br>17 |
| Merck HepB** | 2.5 mcg | 43<br>37<br>47 | 98<br>100<br>98 | 247<br>314<br>647 | 14<br>18<br>19 |
| Merck HepB** | 5.0 mcg | 46 | 100 | 931 | 20 |

*Engerix-B® **Recombivax-HB®

***Conclusion***

This supportive study demonstrated that the change in schedule for the Hep B component (0, 1, 6 months to 2, 4, 6 months) had no significant clinical impact with respect to the immunogenicity elicited by the HepB component as administered in the combination.

### 2.2.3 Overall evaluation of the safety of the SBB DTPa-HepB-IPV vaccine

#### *2.2.3.1 Introduction*

In twelve of the fourteen clinical trials contained in the BLA, a total of 7,028 subjects received 20,739 doses of the DTPa-HepB-IPV. Of the 7,028 infants who received at least one dose of DTPa-HepB-IPV vaccine, safety data are available for a total of 7,000 infants. This includes subjects who received at least one dose of DTPa-HepB-IPV vaccine and for whom at least one symptom sheet was completed (N = 6,995) as well as those subjects for whom a symptom sheet was not completed but for whom information regarding unsolicited adverse experiences is available (N = 5). Of the 6, 995 subjects for whom at least one symptom sheet was completed, 5,344 were eligible for the According-to-Protocol (ATP) analysis of safety.

Most of the subjects excluded from the ATP cohort were subjects who were enrolled in study DTPa-HepB-IPV-011 before an amendment that included randomization versus a newly introduced control group was implemented (1569 out of the 1651 subjects excluded form the overall ATP cohort for safety).

**Table 9: Number of subjects by study who received DTPa-HepB-IPV vaccine with or without Hib vaccine at separate injection sites (Total cohort for safety*)**

| DTPa-HepB-IPV Study: | Age at Vaccination (months) | Received Dose 1 | Received Dose 2 | Received Dose 3 | Total Number of Doses Administered |
|---|---|---|---|---|---|
| 001 | 3, 4, 5 | 20 | 17 | 17 | 54 |
| 002 | 2, 4, 6 | 30 | 29 | 28 | 87 |
| 004 | 2, 4, 6 | 50 | 50 | 49 | 149 |
| 005 | 3, 4, 5 | 567 | 565 | 562 | 1,694 |
| 011 | 3, 4, 5 | 4,695 | 4,638 | 4,593 | 13,926 |
| 012 | 3, 4.5, 6 | 549 | 544 | 543 | 1,636 |
| 015 | 2, 4, 6 | 200 | 188 | 95 | 483 |
| 016 | 3, 4, 5 | 184 | 182 | 180 | 546 |
| 017 | 2, 3, 4 | 29 | 29 | 29 | 87 |
| 019 | 3, 4.5, 6 | 60 | 60 | 57 | 177 |
| 030 | 1.5, 2.5, 3.5 | 160 | 160 | 158 | 478 |
| 044 | 2, 4, 6 | 484 | 470 | 468 | 1,422 |
| **Total** | | **7,028** | **6,932** | **6,779** | **20,739** |

* Subjects who received indicated vaccine dose regardless of whether or not a symptom sheet was completed.

#### *2.2.3.2 Study Objectives*

Studies were designed with the following safety and reactogenicity objectives in mind:

- Assessment of the rates of common solicited adverse events following the administration of the DTPa-HepB-IPV vaccine as compared to that following the individual marketed products administered as separate injections [DTPa-HepB-IPV-015 (USA; control group: DTPa, HepB, and Hib vaccines with OPV vaccine given orally) and DTPa-HepB-IPV-011 (Germany; control group: DTPa and Hib vaccines with OPV vaccine given orally)]. In study DTPa-HepB-IPV-011, the primary objective was to rule out a pre-specified, clinically significant increase (>7.5%) in the proportion of subjects reporting at least one Grade 3 solicited symptom between the pooled DTPa-HepB-IPV vaccine group and the control group.
- Assessment of "less common" adverse events (those occurring at a rate of 1/100) following the administration of the DTPa-HepB-IPV vaccine as compared to that following separate injections of individual marketed products study (DTPa-HepB-IPV-011). The majority of the safety database was sourced from this study in which nearly 5,500 infants received 3 doses of either DTPa-HepB-IPV (N = 4,695), or separate injections of DTPa and Hib vaccines along with OPV vaccine (N = 776).
- Assessment of common solicited adverse events following the Second Lot Series as compared to those following the First Lot Series (DTPa-HepB-IPV-044).
- Assessment of the safety and reactogenicity of the combined vaccine when administered as a three dose primary series following a dose of hepatitis B vaccine given at or shortly after birth, as compared to a three dose primary series in the absence of the birth dose of hepatitis B vaccine (DTPa-HepB-IPV/Hib-003).

#### *2.2.3.3 Assessment of Solicited Adverse Experiences*

In order to evaluate safety and reactogenicity, parents or guardians of the vaccinated children were asked to complete diary cards which specified both local and general adverse experiences (reactogenicity data). Definitions of "severity" (graded 0 to 3) were provided to the parents/guardians for guidance. In addition, space was provided for the recording of other, "unsolicited" signs and symptoms.

In general, studies actively solicited local and general symptoms including the following (depending on the study):

**Table 10: Symptoms solicited – local and general**

| Symptom | Intensity Grade 3* defined as |
|---|---|
| **Local Symptoms** | |
| Pain | preventing normal everyday activities/cried when limb was moved** |
| Redness | Diameter > 20 mm |
| Swelling | Diameter > 20 mm |
| **General Symptoms** | |
| Fever | Rectal temperature > 39.5°C/103.2°F |
| Vomiting | Preventing normal everyday activities |
| Diarrhea | Preventing normal everyday activities |
| Loss of appetite | Preventing normal everyday activities |
| Restlessness/Sleeping less than usual | Preventing normal everyday activities |
| Sleeping more than usual | Preventing normal everyday activities |
| Unusual crying | Preventing normal everyday activities |
| Irritability/fussiness | Preventing normal everyday activities/persistent crying and could not be comforted |

* Grade 3 symptoms considered to be clinically relevant manifestation of symptom

** Cried when limb was moved (studies 044/003)

#### *2.2.3.4 Methods*

##### *Cohorts for Analysis*

All safety analyses were based on the According-to-Protocol (ATP) cohort for safety. These analysis were complemented by "all-data-available" analysis whenever the percentage of subjects excluded from the ATP cohort exceeded 5%.

***Statistical Approach***

In the large, pivotal safety study conducted in Germany (DTPa-HepB-IPV-011), the non-inferiority testing approach evaluated whether or not the limits of the 90% CIs for treatment differences fell within pre-specified clinical acceptability criteria.

This approach was used since concluding non-inferiority cannot be based on a non-statistically significant test for the null hypothesis of no difference between vaccine groups (ICH E-9, Statistical principles for clinical trials, Final, February 1998).

Non-inferiority of DTPa-HepB-IPV relative to a separate injection control group was demonstrated when the upper limit of the 90% CI for the difference in the percentage of subjects with Grade 3 solicited symptoms (whatever the symptom) was below an *a priori* specified clinical limit of non-inferiority of 7.5% (one-sided equivalence test, alpha = 5%, clinical limit = 7.5%).

The non-inferiority approach was also used in study DTPa-HepB-IPV/Hib-003, which evaluated the safety of the combined vaccine following a birth dose of hepatitis B vaccine. The same pre-specified clinical limit of non-inferiority (7.5%) was applied in this study.

### *2.2.3.5 Evaluation Of Common Adverse Events Following Vaccination With DTPa-HepB-IPV Vaccine As Compared To Separate Injections*

Studies DTPa-HepB-IPV-011 and 015 were initiated with the objective of comparing the rates of common solicited adverse events following administration of the DTPa-HepB-IPV vaccine to rates following a control group which consisted of separate injections of commercially available US-licensed vaccines.

#### *2.2.3.5.1 Study DTPa-HepB-IPV-015*

Study DTPa-HepB-IPV-015 was an open, randomized study conducted in the US. This study evaluated the safety of DTPa-HepB-IPV vaccine administered as a three dose series at 2, 4, and 6 months of age. SBB DTPa-HepB-IPV vaccine was co-administered with AP Hib vaccine simultaneously at separate injection sites (Group 1; N=100) as compared to the co-administration of SBB DTPa vaccine, SBB HepB vaccine, AP Hib vaccine and Lederle OPV vaccine (Group 4; N=100).

Table 11 presents the overall incidence of any solicited local symptoms per subject (symptom reported to occur in subject at any dose) during the 4-day follow-up period over the 3 dose primary series. As recognized by the *FDA Guidance for Industry For the Evaluation of Combination Vaccines for Preventable Diseases: Product, Testing and Clinical Studies*, comparison of local adverse reactions is problematic in that local reactions at one injection site for the combination vaccine must be compared to local reactions at more than one site for separately administered component vaccines (an incongruous comparison). Table 11 presents an overall rate that has been calculated for each solicited local symptom reported at any vaccination site. For local symptoms following multiple injections, a symptom was counted once even if reported at multiple sites. **This may therefore underestimate the magnitude of local reactions in both groups, but more so in the separate injection control group.**

The incidence per subject over the three-dose primary series of Grade 3 solicited local symptoms is presented in Table 12.

**Table 11: Incidence of any solicited local symptoms over the 3 dose primary course during the 4-day follow-up period per subject (Study DTPa-HepB-IPV-015)**

| | | Group 1 (N = 100) | | | | Group 4 (N = 98) | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Symptom** | **Vaccine** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** |
| **Pain** | **Overall** | **57** | **57.0** | **46.7** | **66.9** | **51** | **52.0** | **41.7** | **62.2** |
| | DTPa | - | - | - | - | 48 | 49.0 | 38.7 | 59.3 |
| | DTPa-HepB-IPV | 55 | 55.0 | 44.7 | 65.0 | - | - | - | - |
| | HepB | - | - | - | - | 42 | 42.9 | 32.9 | 53.3 |
| | Hib | 40 | 40.0 | 30.3 | 50.3 | 45 | 45.9 | 35.8 | 56.3 |
| **Redness** | **Overall** | **40** | **40.0** | **30.3** | **50.3** | **31** | **31.6** | **22.6** | **41.8** |
| | DTPa | - | - | - | - | 28 | 28.6 | 19.9 | 38.6 |
| | DTPa-HepB-IPV | 35 | 35.0 | 25.7 | 45.2 | - | - | - | - |
| | HepB | - | - | - | - | 17 | 17.3 | 10.4 | 26.3 |
| | Hib | 24 | 24.0 | 16.0 | 33.6 | 19 | 19.4 | 12.1 | 28.6 |
| **Swelling** | **Overall** | **36** | **36.0** | **26.6** | **46.2** | **27** | **27.6** | **19.0** | **37.5** |
| | DTPa | - | - | - | - | 20 | 20.4 | 12.9 | 29.7 |
| | DTPa-HepB-IPV | 31 | 31.0 | 22.1 | 41.0 | - | - | - | - |
| | HepB | - | - | - | - | 8 | 8.2 | 3.6 | 15.5 |
| | Hib | 13 | 13.0 | 7.1 | 21.2 | 14 | 14.3 | 8.0 | 22.8 |

Group 1 = DTPa-HepB-IPV + Hib
Group 4 = DTPa + HepB + Hib + OPV
N = number of subjects with at least one symptom sheet completed
n = number of subjects reporting the specific solicited local symptom
% = percentage of subjects (n/Nx100) reporting the specific solicited local symptom
LL and UL = exact 95% Confidence Interval, lower and upper limit

Overall = local symptom reported for any vaccination site (For local symptoms following multiple injections, a symptom was counted once even if reported at multiple sites.)

**Table 12: Incidence of Grade 3 solicited local symptoms over the 3 dose primary course during the 4-day follow-up period per subject (DTPa-HepB-IPV-015)**

| | | Group 1 (N = 100) | | | | Group 4 (N = 98) | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Symptom** | **Vaccine** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** |
| **Pain** | **Overall** | **3** | **3.0** | **0.6** | **8.5** | **5** | **5.1** | **1.7** | **11.5** |
| | DTPa | - | - | - | - | 5 | 5.1 | 1.7 | 11.5 |
| | DTPa-HepB-IPV | 2 | 2.0 | 0.2 | 7.0 | - | - | - | - |
| | HepB | - | - | - | - | 4 | 4.1 | 1.1 | 10.1 |
| | Hib | 1 | 1.0 | 0.0 | 5.4 | 5 | 5.1 | 1.7 | 11.5 |
| **Redness** | **Overall** | **3** | **3.0** | **0.6** | **8.5** | **1** | **1.0** | **0.0** | **5.6** |
| | DTPa | - | - | - | - | 0 | 0.0 | 0.0 | 3.7 |
| | DTPa-HepB-IPV | 3 | 3.0 | 0.6 | 8.5 | - | - | - | - |
| | HepB | - | - | - | - | 0 | 0.0 | 0.0 | 3.7 |
| | Hib | 0 | 0.0 | 0.0 | 3.6 | 1 | 1.0 | 0.0 | 5.6 |
| **Swelling** | **Overall** | **6** | **6.0** | **2.2** | **12.6** | **3** | **3.1** | **0.6** | **8.7** |
| | DTPa | - | - | - | - | 1 | 1.0 | 0.0 | 5.6 |
| | DTPa-HepB-IPV | 6 | 6.0 | 2.2 | 12.6 | - | - | - | - |
| | HepB | - | - | - | - | 0 | 0.0 | 0.0 | 3.7 |
| | Hib | 1 | 1.0 | 0.0 | 5.4 | 2 | 2.0 | 0.2 | 7.2 |

Group 1 = DTPa-HepB-IPV + Hib
Group 4 = DTPa + HepB + Hib + OPV
N = number of subjects with at least one symptom sheet completed
n = number of subjects reporting the specific solicited local symptom
% = percentage of subjects (n/Nx100) reporting the specific solicited local symptom
LL and UL = exact 95% Confidence Interval, lower and upper limit
Overall = local symptom reported for any vaccination site (For local symptoms following multiple injections, a symptom was counted once even if reported at multiple sites.)
Grade 3 redness and swelling = diameter > 20 mm
Grade 3 pain = pain which prevented normal everyday activities

Group 1 received DTPa-HepB-IPV and Hib vaccines administered at separate sites; Group 4 received US-licensed vaccines administered concomitantly at separate sites. Pain at the injection site was reported by 57.0% (3.0% Grade 3) and 52.0% (5.1% Grade 3) of subjects in Group 1 and Group 4, respectively. Redness at the injection site was observed in 40.0% (3.0% Grade 3) and 31.6% (1.0% Grade 3) of subjects in Group 1 and Group 4, respectively. Swelling at the injection site was observed in 36.0% (6.0% Grade 3) and 27.6% (3.1% Grade 3) of subjects in Group 1 and Group 4, respectively.

The incidence per subject (symptom reported to occur in subject at any dose) over the three-dose primary series of all solicited general symptoms and Grade 3 solicited general symptoms are presented in Tables 13 and Table 14, respectively.

**Table 13: Incidence of all solicited general symptoms during the 4-day follow-up period per subject (Study DTPa-HepB-IPV-015)**

| | Group 1 (N = 100) | | | | Group 4 (N = 98) | | | |
|---|---|---|---|---|---|---|---|---|
| **Symptom** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** |
| Diarrhea | 26 | 26.0 | 17.7 | 35.7 | 28 | 28.6 | 19.9 | 38.6 |
| Fussiness | 82 | 82.0 | 73.1 | 89.0 | 84 | 85.7 | 77.2 | 92.0 |
| Loss of appetite | 38 | 38.0 | 28.5 | 48.3 | 38 | 38.8 | 29.1 | 49.2 |
| Sleeping less than usual | 42 | 42.0 | 32.2 | 52.3 | 42 | 42.9 | 32.9 | 53.3 |
| Sleeping more than usual | 64 | 64.0 | 53.8 | 73.4 | 59 | 60.2 | 49.8 | 70.0 |
| Fever | 41 | 41.0 | 31.3 | 51.3 | 29 | 29.6 | 20.8 | 39.7 |
| Unusual crying | 6 | 6.0 | 2.2 | 12.6 | 6 | 6.1 | 2.3 | 12.9 |
| Vomiting | 13 | 13.0 | 7.1 | 21.2 | 16 | 16.3 | 9.6 | 25.2 |

Group 1 = DTPa-HepB-IPV + Hib
Group 4 = DTPa + HepB + Hib + OPV
N = number of subjects with at least one symptom sheet completed
n = number of subjects reporting the specific solicited general symptom
% = percentage of subjects (n/Nx100) reporting the specific solicited general symptom
LL and UL = exact 95% Confidence Interval, lower and upper limit
Onset on day 0, 1, 2, or 3 following vaccination
Fever = rectal temperature $\geq$ 38.0°C/100.4°F

**Table 14: Incidence of all Grade 3 solicited general symptoms during the 4-day follow-up period per subject (Study DTPa-HepB-IPV-015)**

| | Group 1 (N = 100) | | | | Group 4 (N = 98) | | | |
|---|---|---|---|---|---|---|---|---|
| **Symptom** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** |
| Diarrhea | 2 | 2.0 | 0.2 | 7.0 | 1 | 1.0 | 0.0 | 5.6 |
| Fussiness | 7 | 7.0 | 2.9 | 13.9 | 11 | 11.2 | 5.7 | 19.2 |
| Loss of appetite | 1 | 1.0 | 0.0 | 5.4 | 2 | 2.0 | 0.2 | 7.2 |
| Sleeping less than usual | 1 | 1.0 | 0.0 | 5.4 | 4 | 4.1 | 1.1 | 10.1 |
| Sleeping more than usual | 1 | 1.0 | 0.0 | 5.4 | 2 | 2.0 | 0.2 | 7.2 |
| Fever | 3 | 3.0 | 0.6 | 8.5 | 2 | 2.0 | 0.2 | 7.2 |
| Unusual crying | 0 | 0.0 | 0.0 | 3.6 | 0 | 0.0 | 0.0 | 3.7 |
| Vomiting | 1 | 1.0 | 0.0 | 5.4 | 2 | 2.0 | 0.2 | 7.2 |

Group 1 = DTPa-HepB-IPV + Hib
Group 4 = DTPa + HepB + Hib + OPV
N = number of subjects with at least one symptom sheet completed
n = number of subjects reporting the specific solicited general symptom
% = percentage of subjects (n/Nx100) reporting the specific solicited general symptom
LL and UL = exact 95% Confidence Interval, lower and upper limit
Onset on day 0, 1, 2, or 3 following vaccination
Grade 3 symptom = severity which prevented normal everyday activities
Grade 3 fever = rectal temperature > 39.5°C/103.2°F

Most general adverse events reported were either mild or moderate in intensity. The most frequently reported solicited general symptom was fussiness. In both Groups 1 and 4, 82% or more of the subjects reported fussiness after at least one dose. For some subjects, the presence of fever was not assessed as instructed in the protocol (i.e. a thermometer was not used but the parent/guardian reported a "slight fever"). These "slight fevers" have been included as "any fever" (defined as rectal temperature $\geq$ 38.0°C/100.4°F) in the analysis (N=2 in group 1, N = 0 in group 4). An apparently higher incidence of fever (T $\geq$ 38.0°C/100.4°F) was observed in the DTPa-HepB-IPV vaccine group (41%) when compared to control group (29.6%). However, this difference was not statistically significant. The incidence of grade 3 fever (T > 39.5°C/103.2°F), which did not exceed 3%, was comparable in both groups.

#### *2.2.3.5.2 Study DTPa-HepB-IPV-011*

This study was a large open, randomized comparative study conducted in Germany in which healthy infants between 7 and 18 weeks of age were enrolled to receive a three dose primary series at 3, 4, and 5 months of age. This study was originally designed as an uncontrolled study in which all subjects were randomized to receive SBB DTPa-HepB-IPV vaccine concomitantly at separate sites along with one of four Hib vaccines (manufactured by SBB, AP, Lederle or Merck, respectively) in a 1:1:1:1 fashion. After enrollment of approximately 1600 subjects, the study was amended in order to allow for the introduction of a separate injection control group consisting of SBB DTPa vaccine, AP Hib vaccine, and Lederle OPV vaccine (i.e., US-licensed vaccines served as a separate injection control group for safety). Thus, the remaining 4,000 infants were enrolled and randomized into one of five groups in a 1: 1: 1: 1: 1 ratio [DTPa-HepB-IPV + Hib (SBB): DTP-HepB-IPV + Hib (AP): DTPa-HepB-IPV + Hib (Lederle): DTPa-HepB-IPV + Hib (Merck): DTPa+Hib (AP) + OPV]. An evaluation of the safety of the DTPa-HepB-IPV vaccine as compared to that of separate injections was the primary objective of this study, that is, to rule out a clinically significant increase (>7.5%) in the proportion of subjects reporting at least one solicited symptom rated as Grade 3 in intensity during the 4 day follow-up period following any vaccination (overall vaccination course), between the pooled DTPa-HepB-IPV vaccine groups and the control group.

Table 15 presents the percentage of subjects reporting any Grade 3 solicited symptom over the full vaccination course.

The upper limit of the 90% CI for the difference in the incidence of Grade 3 solicited symptoms was below 7.5% (the *a priori* limit for clinical inferiority). The DTPa-HepB-IPV vaccine group (pooled data from Groups 1-4) can, therefore, be considered to be at least equivalent to the control group (Group 5) with respect to the incidence of Grade 3 solicited symptoms.

It should be noted that infants in the control group received one antigen less (HepB) than infants receiving the candidate DTPa-HepB-IPV vaccine.

**Table 15: Non-inferiority testing of percentage of subjects with Grade 3 solicited symptoms during the 4-day follow-up period over the full course of vaccination (DTPa-HepB-IPV-011)**

| | DTPa-HepB-IPV | | | | Control | | | | Group 1-4 Pooled | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Pooled Groups 1-4* | | | | Group 5 | | | | minus Groups 5 | | |
| | (N=3029) | | | | (N=744) | | | | | | |
| | | | 95% CI | | | | 95% CI | | Difference | 90% CI | |
| **Symptom** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** | **(%)** | **LL** | **UL** |
| Total | 490 | 16.2 | 14.9 | 17.5 | 151 | 20.3 | 17.5 | 23.4 | -4.1 | -7.13 | -1.41# |
| Local | 236 | 7.8 | 6.9 | 8.8 | 90 | 12.1 | 9.8 | 14.7 | -4.3 | -6.83 | -2.15 |
| General | 318 | 10.5 | 9.4 | 11.6 | 94 | 12.6 | 10.3 | 15.2 | -2.1 | -4.74 | 0.11 |

Group 1: DTPa-HepB-IPV + SBB Hib
Group 2: DTPa-HepB-IPV + AP Hib
Group 3: DTPa-HepB-IPV + Lederle Hib
Group 4: DTPa-HepB-IPV + Merck Hib (*Subjects in Group 4 received only 2 doses of Hib vaccine at 3 and 5 months of age)
Group 5: SBB DTPa + AP Hib+ Lederle OPV
N = number of subjects with at least one symptom sheet completed and/or with an unsolicited symptom
n = number of subjects reporting the specific solicited local or general symptom
95% CI, LL and UL = exact 95% Confidence Interval, lower and upper limit
90% CI, LL and UL = exact 90% Confidence Interval, lower and upper limit
Local = local symptom reported for any vaccination site (for local symptoms following multiple injections, a symptom was counted once even if reported at multiple sites)
#upper limit below clinical limit for non-inferiority

The incidences of solicited local symptoms (any grade) were similar in study DTPa-HepB-IPV-015 and study DTPa-HepB-IPV-011, except for the incidence of "any pain" which was higher in study -015 (US population). Additionally, the incidence of solicited local symptoms graded 3 (redness > 20 mm, swelling >20 mm, or pain which prevented normal everyday activities), was similar in both studies. With regard to solicited general symptoms (any grade), the incidence of fever (temperature ≥38.0°C/100.4°F ) was similar in study DTPa-HepB-IPV-015 and study DTPa-HepB-IPV-011. However, the rates of restlessness differed at all doses with higher rates in study -015 than in study -011. Conversely, rates of unusual crying were higher at all 3 doses in study -011 than in study -015. However, for all solicited general symptoms, rates of more clinically meaningful Grade 3 symptoms, including fever, restlessness and unusual crying, were similar in the two studies at all doses.

The incidences of solicited symptoms by dose in study DTPa-HepB-IPV-011 are presented in Table 16. While the incidences of redness and swelling increased from dose 1 to dose 2 at both the DTPa-HepB-IPV and the DTPa injections sites, there were no relevant further increases in the proportion of subjects with local

reactions reported from dose 2 to dose 3. For general solicited symptoms, there were no increases in rates of symptoms observed throughout the primary series.

**Table 16 - Percentage of German infants with local or general symptoms during the 4-day follow-up period following DTPa-HepB-IPV administered concomitantly with Hib at separate sites or DTPa, Hib and OPV at 3, 4, and 5 months of age (Study DTPa-HepB-IPV-011)**

| | **Dose 1** | | **Dose 2** | | **Dose 3** | |
|---|---|---|---|---|---|---|
| | Pooled Groups 1-4 | Group 5 | Pooled Groups 1-4 | Group 5 | Pooled Groups 1-4 | Group 5 |
| No. of infants | 3027 | 744 | 3016 | 738 | 2989 | 731 |
| **Local*** | | | | | | |
| Pain | | | | | | |
| any | 14.2 [13.0, 15.5] | 14.4 [11.9,17.1] | 10.4 [9.4, 11.6] | 9.9 [7.8, 12.3] | 10.3 [9.2, 11.4] | 8.1 [6.2, 10.3] |
| grade 3** | 0.6 [0.4, 1.0] | 1.2 [0.6, 2.3] | 0.3 [0.2, 0.6] | 0.4 [0.1, 1.2] | 0.3 [0.1, 0.6] | 0.1 [0.0, 0.8] |
| Redness | | | | | | |
| any | 18.7 [17.3, 20.1] | 16.4 [13.8, 19.3] | 26.5 [24.9, 28.1] | 21.7 [18.8, 24.8] | 25.9 [24.4, 27.5] | 20.9 [18.0, 24.1] |
| >20 mm | 1.3 [0.9, 1.8] | 1.9 [1.0, 3.1] | 1.0 [0.6, 1.4] | 0.7 [0.2, 1.6] | 1.1 [0.8, 1.5] | 1.1 [0.5, 2.1] |
| Swelling | | | | | | |
| any | 13.6 [12.4, 14.8] | 9.7 [7.6, 12.0] | 18.9 [17.5, 20.3] | 13.1 [10.8, 15.8] | 19.3 [17.9, 20.7] | 14.0 [11.5, 16.7] |
| >20 mm | 1.2 [0.9, 1.7] | 1.3 [0.6, 2.5] | 1.8 [1.3, 2.3] | 1.1 [0.5, 2.1] | 1.6 [1.2, 2.1] | 1.2 [0.6, 2.3] |
| **Systemic** | | | | | | |
| Fever † | | | | | | |
| ≥ 100.4°F | 22.6 [21.1, 24.2] | 13.4 [11.1, 16.1] | 18.2 [16.8, 19.6] | 13.3 [10.9, 15.9] | 19.1 [17.7, 20.5] | 11.2 [9.0, 13.7] |
| > 103.2°F | 0.3 [0.1, 0.5] | 0.1 [0.0, 0.7] | 0.5 [0.3, 0.8] | 0.1 [0.0, 0.8] | 0.8 [0.5, 1.2] | 0.5 [0.1, 1.4] |
| Restlessness | 42.8 [41.0, 44.6] | 46.4 [42.7, 50.0] | 33.2 [31.5, 34.9] | 34.7 [31.3, 38.2] | 27.0 [25.4, 28.6] | 27.5 [24.3, 30.9] |
| Unusual cry | 25.6 [24.0, 27.2] | 36.6 [33.1, 40.1] | 17.5 [16.2, 18.9] | 19.9 [17.1, 23.0] | 13.4 [12.2, 14.7] | 14.2 [11.8, 17.0] |

Group 1: DTPa-HepB-IPV + SBB Hib
Group 2: DTPa-HepB-IPV + AP Hib
Group 3: DTPa-HepB-IPV + Lederle Hib
Group 4: DTPa-HepB-IPV + Merck Hib (*Subjects in Group 4 received only 2 doses of Hib vaccine at 3 and 5 months of age)
Group 5: SBB DTPa + AP Hib + Lederle OPV
*Local = local symptom reported for DTPa-HepB-IPV site in Groups 1-4 & DTPa site in Group 5

** Grade 3 pain = pain which prevented normal everyday activities

† Rectal temperatures

#### *2.2.3.5.3 Evaluation of Fever Following Vaccination with DTPa-HepB-IPV Vaccine as Compared to Separate Injections*

In order to assess the clinical relevance of the higher rate of **low-grade** fever in DTPa-HepB-IPV recipients as compared to control vaccine recipients, the following factors were evaluated:

- duration of fever
- antipyretic use
- withdrawals for adverse events
- cases of sepsis or sepsis work-up within seven days after vaccination
- cases of febrile seizures occurring within seven days after vaccination
- hospitalizations for fever within seven days after vaccination

***Duration of fever (Studies DTPa-HepB-IPV-011 and 015)***

No differences in duration of fever were found between DTPa-HepB-IPV vaccine recipients and separate injection control vaccine recipients in the comparative studies. The vast majority of the cases lasted for one or two days, and more than 98.5% resolved during the four day solicited follow-up period.

***Antipyretic Use (Studies DTPa-HepB-IPV-011, 015 and 044)***

The use of antipyretics was also analyzed in the large German safety study DTPa-HepB-IPV-011 as well as in the two US studies DTPa-HepB-IPV-015 and DTPa-HepB-IPV-044.

The results show that in all studies there were no major differences in the overall use of antipyretic usage over the three dose vaccination course in the groups that received DTPa-HepB-IPV vaccine co-administered with Hib vaccine as compared to the control vaccine regimens. There were no differences in prophylactic use of antipyretics across groups over the three dose vaccination course. Most antipyretic medications were given to treat solicited symptoms after vaccination (fever, restlessness, fussiness). Therefore, as they were given therapeutically, they would not be expected to influence the incidence of fever reported.

***Withdrawals for adverse events (DTPa-HepB-IPV-011)***

The incidence of adverse events leading to withdrawal was 0.2% in both DTPa-HepB-IPV vaccine recipients and control separate injection vaccine recipients in the large safety study DTPa-HepB-IPV-011. Most AEs which lead to subject withdrawal were serious adverse events which were felt to be unrelated to vaccination.

The results of these additional analyses confirm that the observed increase in low grade fever does not result in clinically relevant consequences.

***Sepsis Work-up (Studies DTPa-HepB-IPV-011, 015 and 044)***

In total, four cases of sepsis or sepsis work-up were identified. Two of the four cases occurred within seven days following vaccination, both in DTPa-HepB-IPV vaccine recipients. Both occurred in 2 month old infants following dose one. In study DTPa-HepB-IPV-015, one subject had onset of fever 4 days after vaccination associated with decreased appetite and rash. The subject was hospitalized for two days with a diagnosis of viral syndrome (CSF, blood and urine culture negative) considered by the investigator to be unrelated to vaccination. No further doses of study vaccine were given. In study DTPa-HepB-IPV-044, one subject had onset of a low grade fever one day prior to vaccination and was afebrile on the day of vaccination but the following day developed a fever of 100.8°F, associated with lethargy. He was hospitalized for three days with CSF and blood cultures negative. The fever was considered to be possibly related to vaccination. He completed the three dose primary course uneventfully.

***Febrile Seizures (Studies DTPa-HepB-IPV-011, 015 and 044)***

One case involving febrile seizures within seven days after vaccination was identified in study DTPa-HepB-IPV-011. The seizures were considered unrelated to the vaccination by the investigator and were attributed to a convulsive disorder (diagnosis included febrile convulsions, atonic afebrile convulsions, and suspected hepatopathy and myocarditis). The child died one month later.

***Hospitalizations with Fever ≥ 38.5°C/101.3°F***

A total of 7 subjects were hospitalized with fever (rectal temperature ≥ 38.5°C/101.3°F) within 7 days of vaccination among 4695 (0.15%) DTPa-HepB-IPV vaccine recipients. In the control vaccine recipients, 3 subjects were hospitalized with fever among 776 recipients (0.39%).

### *2.2.3.6 Evaluation Of Common Adverse Events Following Vaccination With The Second Lot Series As Compared To The First Lot Series*

In addition to an assessment of lot consistency for the Second Lot series of DTPa-HepB-IPV vaccine, study DTPa-HepB-IPV-044 was designed to evaluate the safety and reactogenicity following administration of the Second Lot series (data from the 3 lots pooled, Groups 1 - 3) to that following administration of the First Lot series (Group 4).

The observed incidence of solicited local and general symptoms was similar between the first Lot Series (Groups 1, 2 and 3 pooled) and the Second Lot Series (Group 4) for any symptoms, including Grade 3 symptoms (data not shown).

### *2.2.3.7 Evaluation Of Common Adverse Events Following Vaccination With Three Doses Of Combined DTPa-HepB-IPV Vaccine Following A Birth Dose Of Hepatitis B Vaccine*

As the first dose of hepatitis B vaccine may be given at birth according to the US schedule, it is possible that after licensure of a DTPa-HepB-IPV combination vaccine a child could receive 4 doses of hepatitis B vaccine during the first 6 months of life (i.e., birth, 2, 4, and 6 months of age).

Therefore, this clinical study was undertaken to demonstrate that three doses of SBBs' DTPa-HepB-IPV/Hib vaccine administered at 2, 4 and 6 months of age following a birth dose of Engerix-B® at 0 to 14 days of age is at least as safe as three doses of SBBs' DTPa-HepB-IPV/Hib vaccine administered at 2, 4 and 6 months of age without a birth dose of hepatitis B vaccine, ruling out a 7.5% increase (considered clinically significant) in subjects reporting any solicited symptoms ("grade 3") over the three dose primary course. In this clinical study, the combined DTPa-HepB-IPV vaccine was extemporaneously mixed and given in a single injection with Hib tetanus toxoid conjugate vaccine. Please note, this study was designed (and discussed with FDA) to support both the DTPa-HepB-IPV and DTPa-HepB-IPV/Hib products.

Table 17 provides the incidence of any solicited local and general symptoms per subject over the primary vaccination course for both study groups, showing that the symptom-specific reaction rates were comparable between the two groups. As can be seen in Table 18, the primary objective of the study was met; a birth dose of hepatitis B vaccine did not result in an increase in grade 3 reactions over the three dose primary course.

**Table 17: Incidence of solicited local and general symptoms per subject during the 8 day follow-up period over the DTPa-HepB-IPV/Hib primary course - ATP cohort for safety (Study DTPa-HepB-IPV/Hib-003)**

| | Group 1 (N = 259) | | | | Group 2 (N = 265) | | | |
|---|---|---|---|---|---|---|---|---|
| **Symptom** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** |
| **Local** | | | | | | | | |
| Pain | 172 | 66.4 | 60.3 | 72.1 | 147 | 55.5 | 49.3 | 61.6 |
| Redness | 168 | 64.9 | 58.7 | 70.7 | 156 | 58.9 | 52.7 | 64.9 |
| Swelling | 149 | 57.5 | 51.3 | 63.6 | 128 | 48.3 | 42.1 | 54.5 |
| **General** | | | | | | | | |
| Fever | 152 | 58.7 | 52.4 | 64.7 | 143 | 54.0 | 47.8 | 60.1 |
| Drowsiness | 202 | 78.0 | 72.4 | 82.9 | 200 | 75.5 | 69.8 | 80.5 |
| Irritability/Fussiness | 225 | 86.9 | 82.1 | 90.7 | 235 | 88.7 | 84.2 | 92.2 |
| Loss of appetite | 149 | 57.5 | 51.3 | 63.6 | 147 | 55.5 | 49.3 | 61.6 |

Group 1 = DTPa-HepB-IPV/Hib without HepB at birth
Group 2 = DTPa-HepB-IPV/Hib with HepB at birth
N = number of subjects with at least one symptom sheet completed
n = number of subjects reporting the specific solicited general symptom
% = percentage of subjects (n/Nx100) reporting the specific solicited general symptom
LL and UL = exact 95% Confidence Interval, lower and upper limit
Fever = rectal temperature ≥ 38.0°C/100.4°F

**Table 18: Percentage of subjects with Grade 3 solicited symptoms during the 8-day follow-up period over the full DTPa-HepB-IPV/Hib primary course of vaccination (Study DTPa-HepB-IPV/Hib-003)**

| | Group 1 (N=259) | | | | Group 2 (N=265) | | | | Group 2 minus Group 1 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 95% CI | | | | 95% CI | | Difference | 90% CI | |
| **Symptom** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** | **(%)** | **LL** | **UL** |
| Total | 60 | 23.2 | 18.2 | 28.8 | 60 | 22.6 | 17.7 | 28.2 | -0.5 | -7.4 | 6.1* |
| Local | 34 | 13.1 | 9.3 | 17.9 | 24 | 9.1 | 5.9 | 13.2 | -4.1 | -9.0 | 1.2 |
| General | 31 | 12.0 | 8.3 | 16.6 | 45 | 17.0 | 12.7 | 22.1 | 5.0 | -0.6 | 11.2 |

Group 1 = DTPa-HepB-IPV/Hib without HepB at birth
Group 2 = DTPa-HepB-IPV/Hib with HepB at birth
N = number of subjects with at least one symptom sheet completed and/or with an unsolicited symptom
n = number of subjects reporting the specific solicited local or general symptom
95% CI, LL and UL = exact 95% Confidence Interval, lower and upper limit
90% CI, LL and UL = exact 90% Confidence Interval, lower and upper limit
*Upper limit below clinical limit for non-inferiority

### *2.2.3.8 Unsolicited Adverse Experiences*

In the pivotal safety study (DTPa-HepB-IPV-011), a secondary objective was to evaluate "less frequent" AEs, that is, those occurring at a rate of 1/100. Rates of unsolicited symptoms, including symptoms occurring at a rate of 1% or less, were similar in those receiving DTPa-HepB-IPV +Hib vaccine as compared to those receiving separate injections of each component.

An unsolicited AE included any noxious, pathological, or unintended change in anatomical, physiological, or metabolic function as indicated by physical signs, symptoms, and/or laboratory changes which occurred in any phase of the clinical studies whether associated with DTPa-HepB-IPV vaccine or active comparator and whether or not considered vaccine-related. This included an exacerbation of a pre-existing condition or event, intercurrent illness or drug interaction. Anticipated day-to-day fluctuations of the patient's pre-existing conditions were not considered AEs. Discrete episodes of chronic conditions which occurred during a study period were reported as AEs in order to assess changes in frequency or severity.

The recording of AEs was an important aspect of the study documentation. The majority of the studies recorded unsolicited AEs for a period of up to 30 days after each vaccination. The three body systems (by the WHO body system code) with the greatest percentage of subjects reported to have experienced adverse events were Resistance Mechanism (30.3%, reflecting upper respiratory tract infections, otitis media, moniliasis, etc), Respiratory (27.9%), and Gastrointestinal (17.0%). The most common unsolicited events reported following vaccination were bronchitis (9.9%), upper respiratory tract infection (9.7%) and fever (7.0%). Overall, there was a very low incidence (1.7%) of DTPa-HepB-IPV-vaccinated subjects reported to have experienced grade 3 unsolicited AEs (defined as adverse events which prevented normal, everyday activities, i.e. more clinically relevant AEs).

Incidences of frequent ($\geq$ 1%) unsolicited adverse experiences observed in study DTPa-HepB-IPV-011 are shown in Table 19.

**Table 19: Frequent (≥1%) unsolicited adverse experiences, by WHO Body System and Preferred Term, reported during the 30-day follow-up period after vaccination – Per subject summary (Study DTPa-HepB-IPV-011)**

| | | Pooled Groups 1-4* | | Group 5 | | Group 5 minus |
|---|---|---|---|---|---|---|
| | | N=3029 | | N=744 | | Pooled Groups1-4 |
| **WHO Body System (Code)** | **WHO Preferred Term (Code)** | **n ( % )** | **95% CI** | **n ( % )** | **95% CI** | **Difference [90% CI]** |
| Application site (1820) | Dermatitis contact (0049) | 161 (5.3%) | [4.5%,6.2%] | 33 (4.4%) | [3.1%, 6.2%] | -0.9% [-2.3%,0.5%] |
| | Injection site mass (0055) | 33 (1.1%) | [0.8%,1.5%] | 9 (1.2% ) | [0.6%, 2.3%] | 0.1% [-0.6% ,0.8%] |
| | Injection site reaction (0058) | 64 (2.1%) | [1.6%,2.7%] | 16 (2.2%) | [1.2%, 3.5% ] | 0.0% [-0.9%,1.0%] |
| Body as a whole general (1810) | Fatigue (0724) | 76 (2.5%) | [2.0%,3.1% ] | 14 (1.9%) | [1.0%, 3.1% ] | -0.6% [-1.6% ,0.3%] |
| | Fever (0725) | 255 (8.4%) | [7.5%,9.5%] | 65 (8.7%) | [6.8%, 11.0%] | 0.3% [-1.6% ,2.2%] |
| Gastrointestinal (600) | Abdominal pain (0268) | 36 (1.2%) | [0.8%,1.6%] | 13 (1.7%) | [0.9%, 3.0%] | 0.6% [ -0.3% ,1.4% ] |
| | Constipation (0204) | 57 (1.9%) | [1.4%,2.4%] | 12 (1.6%) | [0.8%, 2.8%] | -0.3% [ -1.1% ,0.6%] |
| | Diarrhea (0205) | 52 (1.7%) | [1.3%,2.2%] | 12 (1.6%) | [0.8%, 2.8%] | -0.1% [ -1.0% ,0.8%] |
| | Enteritis (0282) | 84 (2.8%) | [2.2% ,3.4%] | 20 (2.7%) | [1.7%, 4.1%] | -0.1% [ -1.2% ,1.0%] |
| | Gastroenteritis (0293) | 115 (3.8%) | [3.1% ,4.5%] | 24 (3.2%) | [2.1%, 4.8%] | -0.6% [ -1.8% ,0.6%] |
| | Tooth ache (1376) | 65 (2.1%) | [1.7% ,2.7%] | 22 (3.0%) | [1.9%, 4.4%] | 0.8% [ -0.3% ,1.9%] |
| | Vomiting (0228) | 52 (1.7%) | [1.3% ,2.2%] | 8 (1.1%) | [0.5%, 2.1%] | -0.6% [ -1.4% ,0.1%] |
| Psychiatric (500) | Insomnia (0183) | 38 (1.3%) | [0.9% ,1.7%] | 8 (1.1%) | [0.5%, 2.1%] | -0.2% [ -0.9% ,0.5%] |
| | Nervousness (0188) | 66 (2.2%) | [1.7% ,2.8%] | 17 (2.3%) | [1.3%, 3.6%] | 0.1% [ -0.9% ,1.1%] |
| | Somnolence (0197) | 109 (3.6%) | [3.0% ,4.3%] | 22 (3.0%) | [1.9%, 4.4%] | -0.6% [ -1.8% ,0.5 ] |
| Resistance mechanism (1830) | Varicella (0862) | 33 (1.1%) | [0.8%, 1.5%] | 7 (0.9%) | [0.4%, 1.9%] | -0.1% [-0.8%, 0.5%] |
| | Infection (0736) | 110 (3.6%) | [3.0%, 4.4%] | 31 (4.2%) | [2.9%, .9%] | 0.5% [-0.8%, 1.9%] |
| | Infection bacterial (0738) | 18 (0.6%) | [0.4%, 0.9%] | 8 (1.1%) | [0.5%, 2.1%] | 0.5% [-0.2%, 1.1%] |
| | Infection viral (0740) | 180 (6.0%) | [5.1%, 6.9%] | 43 (5.8%) | [4.2%, 7.7%] | -0.2% [-1.7%, 1.4%] |
| | Monoliasis (0741) | 162 (5.4%) | [4.6%, 6.2%] | 30 (4.0%) | [2.7%, 5.7%] | -1.3% [-2.7%, 0.0%] |
| | Otitis media (0750) | 154 (5.1%) | [4.3%, 5.9%] | 37 (5.0%) | [3.5%, 6.8%] | -0.1% [-1.6%, 1.4%] |
| | Upper respiratory tract infection (0543) | 252 (8.3%) | [7.4%, 9.4%] | 60 (8.1%) | [6.2%, 10.3%] | -0.3% [-2.1%, 1.6%] |
| Respiratory (1100) | Bronchitis (0805) | 376 (12.4%) | [11.3% ,13.7%] | 73 (9.8%) | [7.8% ,12.2%] | -2.6% [-4.7%, -0.6%] |

| | | Pooled Groups 1-4* | | Group 5 | | Group 5 minus |
|---|---|---|---|---|---|---|
| | | N=3029 | | N=744 | | Pooled Groups1-4 |
| **WHO Body System (Code)** | **WHO Preferred Term (Code)** | **n ( % )** | **95% CI** | **n ( % )** | **95% CI** | **Difference [90% CI]** |
| | Coughing (0513) | 55 (1.8%) | [1.4%, 2.4% ] | 18 (2.4%) | [1.4%, 3.8%] | 0.6% [-0.4%, 1.6%] |
| | Laryngitis (0521) | 34 (1.1%) | [0.8%, 1.6% ] | 10 (1.3%) | [0.6%, 2.5%] | 0.2% [-0.5%, 1.0%] |
| | Pharyngitis (0523) | 66 (2.2%) | [1.7%, 2.8%] | 16 (2.2%) | [1.2%, 3.5%] | -0.0% [-1.0%, 1.0%] |
| | Respiratory disorder (0536) | 168 (5.6%) | [4.8%, 6.4%] | 46 (6.2%) | [4.6%, 8.2%] | 0.6% [-1.0%, 2.2%] |
| | Rhinitis (0539) | 165 (5.5% ) | [4.7%, 6.3%] | 42 (5.7%) | [4.1%, 7.6%] | 0.2% [-1.4%, 1.7%] |
| Skin and appendages (100) | Dermatitis (0007) | 120 (4.0% ) | [3.3%, 4.7%] | 28 (3.8%) | [2.5%, 5.4%] | -0.2% [-1.5%, 1.1%] |
| | Eczema (0012) | 107 (3.5% ) | [2.9%, 4.3%] | 26 (3.5%) | [2.3%, 5.1%] | -0.0% [-1.3%, 1.2%] |
| | Rash erythematous (0028) | 29 (1.0% ) | [0.6%, 1.4%] | 5 (0.7%) | [0.2%, 1.6%] | -0.3% [-0.9%, 0.3%] |
| Vision (431) | Conjunctivitis (0238) | 128 (4.2% ) | [3.5%, 5.0%] | 39 (5.2%) | [3.8%, 7.1%] | 1.0% [-0.5%, 2.5%] |

Group 1: DTPa-HepB-IPV + SBB Hib
Group 2: DTPa-HepB-IPV + AP Hib
Group 3: DTPa-HepB-IPV + Lederle Hib
Group 4: DTPa-HepB-IPV + Merck Hib (*Subjects in Group 4 received only 2 doses of Hib vaccine at 3 and 5 months of age)
Group 5: SBB DTPa + PM Hib + Lederle OPV
N = number of subjects with a completed solicited symptom sheet and/or for whom an unsolicited symptom was reported
n = number of subjects who were reported to have experienced the symptom
90% CI, LL and UL = asymptotic 90% Confidence Interval, lower limit and upper limit
95% CI, LL and UL = exact 95% Confidence Interval, lower and upper limit

#### *2.2.3.9 Serious Adverse Experiences – All Studies*

There were eight serious adverse experiences (SAEs) reported by the investigators as "related", "probably related", "possibly related" or "suspected to be related" to study vaccination among the 7,028 DTPa-HepB-IPV recipients in the 12 completed studies involving DTPa-HepB-IPV contained in the BLA. Six of these eight SAEs involved fever with or without restlessness or a change in behavior, beginning within three days post-vaccination. For three of the six cases of fever, a possible alternative cause of the fever was given. In a fourth case, fever was noted to be present on the day prior to vaccination. One SAE involved an urticarial rash which began two days post-vaccination and one case involved crying associated with a reaction at the Hib vaccine injection site (one case of fever also involved pain at the Hib vaccine injection site).

No unusual pattern or symptom complex was identified for any of the SAEs.

#### *2.2.3.10 Withdrawals Due to Adverse Experiences – All Studies*

Of the 7,028 subjects who received one or more doses of the DTPa-HepB-IPV vaccine, the number of subjects who subsequently withdrew due to an AE in the 12 completed clinical trials contained in the BLA was relatively low (N = 15) (Table 20). Only three of the 15 AEs were reported as related or possibly related to vaccination. All three were reported as Serious Adverse Experiences, all of which involved a fever which was temporally associated with vaccination. However, for two of the three cases, a possible alternative cause for fever was reported.

No other particular pattern of events leading to withdrawal was apparent.

**Table 20: Subjects who received DTPa-HepB-IPV vaccine and were withdrawn due to an adverse experience**

| Study | Adverse experience | Serious?Y/N | Relationship* | Outcome |
|---|---|---|---|---|
| 002 | Sudden Infant Death Syndrome | Y | PU | Died |
| 011 | Febrile Reaction, Suspicion of Influenza Infection | Y | PR | Recovered |
| 011 | Febrile Convulsion, Atonic Afebrile Convulsions, Suspected Hepatopathy, Suspected Myocarditis | Y | U | Died |
| 011 | Hypoxic Cerebral Damage, Febrile Convulsions, Septicopyemia | Y | U | Died |
| 011 | Enteritis, Respiratory Infection, Tonsillitis | N | U | Recovered |
| 011 | Infantile Nodding Spasms, Gastroenteritis | Y | U | Ongoing |
| 011 | Allergic Reaction to Vegetables | Y | U | Recovered |
| 011 | Idiopathic West Syndrome | Y | U | Recovered |
| 011 | Psychosomatic Excitation | Y | U | Unknown |
| 011 | Sudden Infant Death Syndrome | Y | U | Died |
| 011 | Very High Fever | Y | R | Recovered |
| 012 | Hyperthermic Reaction<br>Acute Gastroenterocolitis, Acute Respiratory Infection, Bronchitis | Y<br>Y | R<br>U | Recovered<br>Recovered |
| 015 | Neuroblastoma | Y | U | Died |
| 015 | Seizure Disorder | Y | U | Recovered |
| 044 | Popping Noise in Multiple Joints | Y | PU | Recovered |

*Different studies employed different attribution terms for relationship. The categories have been consolidated as: U = Unrelated, PU = Probably unrelated/Unlikely to be related, PR = Possibly related, SU = Suspected to be related, PB = Probably related, R = Related

### *2.2.3.11 Deaths – All Studies*

There were six deaths reported during the course of the 12 DTPa-HepB-IPV trials contained in the BLA and two deaths reported during ongoing or completed studies not contained in the BLA for a total of eight deaths. All eight deaths were considered unrelated or probably unrelated to vaccination. Five of the deaths occurred in subjects who received DTPa-HepB-IPV vaccine with or without Hib vaccine in the BLA studies (total N in file = 7,028). Causes of death in DTPa-HepB-IPV vaccine recipients included 2 cases of Sudden Infant Death Syndrome (SIDS)*, and one each of the following: convulsive disorder, congenital immunodeficiency with sepsis, and neuroblastoma.

> ***** *The rate of SIDS observed in the large German safety study (DTPa-HepB-IPV-011) was 0.2/1,000 vaccinated infants (reported rate of SIDS in Germany in a 1998 report was 1-5/1,000 newborns). The reported rate of SIDS in the U.S. from 1990 to 1994 was 1.2/1,000 live births [6, 7].*

Three deaths occurred in subjects who received a control vaccine regimen [1 in a BLA study (total N in file =1764) and 2 in an ongoing study not contained in the BLA]. Causes of death in control vaccine regimens included one case of SIDS, one case of bronchoaspiration, and one case of respiratory failure due to pneumonia.

It is also important to note that no cases of hypotonic hyporesponsiveness, encephalopathy, or anaphylaxis were reported.

## 2.3 Clinical Conclusions

The clinical development of the candidate DTPa-HepB-IPV vaccine was conducted to support the proposed indication and to address the recommendations outlined in the *FDA Guidance for Industry For Evaluation of Combination Vaccines for Preventable Diseases: Production, Testing and Clinical Trials (April 1997*).

In twelve of the clinical trials contained in the original BLA, a total of 7, 028 subjects received 20,739 doses of the DTPa-HepB-IPV vaccine. Immunogenicity data were reviewed from eleven out of the twelve studies; in the twelfth study, only safety was evaluated. In a thirteenth study (DTPa-HepB-IPV/Hib-003), conducted in the U.S. and also submitted to the BLA during review, the impact of a dose of hepatitis B vaccine given at or shortly after birth on the subsequent primary series of DTPa-HepB-IPV/Hib was evaluated. The change in schedule for the HepB component when given as a part of SBB's DTPa-HepB vaccine was evaluated in a fourteenth study (also contained in the original BLA).

The following major conclusions can be drawn from the results of the aforementioned studies:

- The SBB DTPa-HepB-IPV vaccine was immunogenic for all vaccine antigens in all study populations when administered as a three dose primary series according to a variety of vaccination schedules beginning as early as 6 weeks of age.

- Three doses of DTPa-HepB-IPV vaccine were shown to be comparably immunogenic to US-licensed DTPa, HepB and OPV vaccines administered separately in an open, randomized study in the US. The vaccine was also shown to be comparably immunogenic to three doses of separately administered U.S.-licensed IPV vaccine.

- The First Lot and Second Lot Series of the SBB DTPa-HepB-IPV vaccine were shown to produce a consistent immune response for all antigens contained in the vaccine.

- The Second Lot Series produced following a manufacturing change was shown to be at least as immunogenic as the First Lot Series in terms of all parameters of primary interest.

- SBB DTPa-HepB-IPV vaccine and licensed Hib vaccines are highly immunogenic for all antigens when co-administered separately.

- The comparability in terms of seroprotection to the HepB component as part of a combination vaccine given at 2, 4, and 6 months of age to that of SBB HepB vaccine given according to a US-licensed regimen (0, 1, 6 months) was demonstrated in a study conducted in the U.S.

- Assessment of the rates of common solicited adverse events following the administration of the DTPa-HepB-IPV vaccine as compared to that following the individual marketed products administered as separate injections was done in two studies [DTPa-HepB-IPV-015 (USA) and DTPa-HepB-IPV-011 (Germany)]. In study DTPa-HepB-IPV-011, the primary objective was to rule out a pre-specified, clinically significant increase (>7.5%) in the proportion of subjects reporting at least one Grade 3 solicited symptom between the pooled DTPa-HepB-IPV vaccine group and the control group. This primary objective was met.

- Rates of unsolicited symptoms including those occurring at a rate of 1% or less were similar in those receiving DTPa-HepB-IPV vaccine as compared to those receiving separate injections.

- The incidence of common solicited adverse events was comparable between the Second Lot series and the First Lot series.

- The safety of administration of DTPa-HepB-IPV on a primary series schedule following a birth dose of hepatitis B vaccine was demonstrated (via a study with DTPa-HepB-IPV/Hib).

- No unusual pattern or symptom complex was identified for any of the SAEs reported in any study supporting this product.

Overall, the DTPa-HepB-IPV vaccine has been shown to be immunogenic for the three-dose primary series indication. The vaccine is well-tolerated, and is at least as safe as the individual routinely administered US-licensed vaccines. The combination of antigens does not appear to place vaccinees at an increased risk of adverse events.

Finally, the fewer injections required as a result of administration of the DTPa-HepB-IPV vaccine in the primary vaccination series is anticipated to lead to an increase in compliance and offers the additional benefit of decreasing the discomfort associated with multiple injections given to infants at a single office visit.

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# Appendix I

List of Abbreviations

| Abbreviation | Description |
|---|---|
| 69k | Pertactin, 69k outer membrane protein |
| 2ϕEtOH/or 2-PE | 2-Phenoxyethanol |
| AAP | American Academy of Pediatrics |
| ACIP | Advisory Committee on Immunization Practices |
| ads | adsorbed |
| Ag | Antigen |
| Anti-PT | Antibody to pertussis toxoid component |
| Anti-FHA | Antibody to filamentous haemagglutinin component |
| Anti-PRN | Antibody to pertactin component |
| ATP | According to Protocol Analysis |
| AP | Aventis Pasteur Serums et Vaccins or Aventis Pasteur, Inc. |
| BLA | Biologics License Application |
| CB | Chiron Behring GmbH |
| CBER | Center for Biologics Evaluation and Research |
| CI | Two-sided Confidence Interval |
| CMC | Chemistry, Manufacturing and Controls |
| D | Diphtheria |
| DT | Diphtheria and tetanus toxoids, adsorbed |
| DTPa | Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine, Adsorbed |
| DTPa-HepB-IPV | Diphtheria, Tetanus, Acellular Pertussis, Hepatitis B vaccine (recombinant) and Inactivated Poliovirus Vaccine |
| DU | D-antigen Unit |
| ELISA | Enzyme-linked immunosorbent assay |
| *Engerix-B*® | Hepatitis B Vaccine, Recombinant |
| EL.U. | ELISA Units |
| FDA | Food and Drug Administration |
| FHA | Filamentous haemagglutinin |
| GMT | Geometric Mean Titre |
| GMU | Geometric mean unit |
| GSK | GlaxoSmithKline (umbrella entity following recent merger – includes SB, SBB, SBB Manufacturing) |
| HepB/HB or HBV | Hepatitis B Vaccine (or to identify the antigen alone) |
| HBsAg | Hepatitis B surface antigen |
| Hib | *Haemophilus influenzae* type b |
| IND | Investigational New Drug Application |
| IPV | Inactivated poliovirus vaccine |
| IU | International Units |

| Abbreviation | Description |
|---|---|
| IgG | Immunoglobulin G |
| *Infanrix*® | Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine, Adsorbed |
| *Infanrix*®$_{DTPa}$-HepB-IPV | Formal Brand Name for product |
| ITT | Intent-to-treat Analysis |
| Lf | Limit flocculation |
| mg | Milligram |
| mL | Milliliter |
| Merck or Merck's | Merck & Co. |
| NIH | National Institutes of Health |
| OMP | Outer membrane protein |
| OPV | Oral polio vaccine |
| Pa | Acellular pertussis |
| PLA | Product License Application |
| PRN | Pertactin, 69K outer membrane protein |
| PT | Pertussis toxoid |
| QA | Quality Assurance |
| QC | Quality Control |
| SB | SmithKline Beecham Pharmaceuticals (a GlaxoSmithKline Co.) |
| SBB | SmithKline Beecham Biologicals (a GlaxoSmithKline Co.) |
| SBB Mfg | SmithKline Beecham Biologicals Manufacturing (a GlaxoSmithKline Co.) |
| SOP | Standard operating procedures |
| SP | Seroprotection |
| T | Tetanus |
| ug or µg or mcg | microgram |
| VR | Vaccine response |
| WHO | World Health Organization |

# Appendix II

## Worldwide Marketing Information

**SBB Combination Products**

**Containing antigenic components of**

**DTPa-HepB-IPV**

**Table 21 – Worldwide Marketing Information: DTPa-based combinations & *Engerix-B***

| Vaccine | Countries Licensed (Marketed) | Doses Distributed | Year of 1st Registration |
|---|---|---|---|
| DTPa (*Infanrix®*) Vaccine | 69 (52) | >31 million | 1996 |
| HepB (*Engerix-B®*) Vaccine | 145 | >500 million | 1986 |
| DTPa-HepB-IPV Vaccine | 17 (0) | 0* | 2000 |
| DTPa-HepB-IPV/Hib Vaccine (admixed) | 19 (2) | >0.2 million | 2000 |
| DTPa-HepB Vaccine | 44 (7) | >2.7 million | 1997 |
| DTPa/Hib Vaccine | 30 (9) | >6.4 million | 1996 |
| DTPa-IPV Vaccine | 6 (3) | >1.0 million | 1996 |
| DTPa-IPV/Hib Vaccine | 36 (15) | > 7.4 million | 1998 |

*Marketing imminent in Italy; expanded commercialization not anticipated due to preference for DTPa-HepB-IPV/Hib

# Appendix III

## Efficacy Information

**Infanrix®**
**&**
**Engerix-B®**

**Established Efficacy of *Infanrix* and *Engerix-B* Vaccines**

The DTPa-HepB-IPV combination vaccine contains antigens manufactured by the identical process to that employed for the U.S.-licensed *Infanrix* product and hepatitis B surface antigen manufactured in nearly the same fashion (see Section 2.0 for details) as that employed for the production of U.S.-licensed *Engerix-B*. These products were licensed based upon well controlled studies of protective efficacy.

As per FDA's *Guidance for Industry For the Evaluation of Combination Vaccines for Preventable Diseases: Production, Testing and Clinical Studies (April 1997),* reference to these efficacy studies has been made in the BLA for DTPa-HepB-IPV vaccine. In this context, the immunogenicity data presented in this briefing document and in the BLA under FDA review, are being used to bridge to the existing efficacy data for *Infanrix* and *Engerix-B*. Additionally, although efficacy of the poliovirus (IPV) component in the combination vaccine has not specifically been established, the immunogenicity demonstrated by the IPV component in the combination has been compared in a clinical trial to that of a US-licensed inactivated poliovirus vaccine (IPOL®).

The following tables reference the studies, previously approved under the existing product licenses for the aforementioned products, conducted to demonstrate efficacy of these individual products.

**Table 22:** Efficacy Trials with Infanrix®

| Protocol No. | Title |
|---|---|
| NIH Italian Efficacy Study | Efficacy Trial of an Acellular Pertussis Vaccine in Italy. |
| APV-050 | Prospective Household Contact Study to compare the frequency of clinical pertussis disease following household exposure in children previously vaccinated with a primary course of 3 doses of SmithKline Beecham Biologicals' combined acellular tricomponent DTPa vaccine and in children not immunized against pertussis. |

This SBB DTPa vaccine was shown in an SBB household contact study of vaccine efficacy, conducted in Germany, to have a protective efficacy of 88.7% (95% CI: 76.6%–94.6%) against typical pertussis as defined by the WHO (spasmodic cough ≥21 days duration, with laboratory confirmation [8]; when administered as a three-dose primary vaccination course at 3, 4 and 5 months of age [9].

The protective efficacy of the SBB DTPa vaccine as a three-dose primary vaccination at 2, 4 and 6 months of age has also been evaluated in a large placebo-controlled prospective cohort study conducted in Italy under the auspices of the US National Institute of Allergy and Infectious Diseases (NIAID). In this study, SBB DTPa was shown to have an efficacy of 83.9 % (95 % CI: 75.8–89.4) against WHO-defined pertussis [10], a finding which correlates well with that of the SBB German household contact study. Follow-up of subjects included in this study for up to 54 months after vaccination has shown no decrease in vaccine efficacy over this period [11].

**Table 23:** Efficacy Trials with Engerix-B®

| **Protocol No.** | **Title** |
|---|---|
| HBV-015 | A study of the reactogenicity, immunogenicity, and protective efficacy of three doses (20mcg or 40mcg) of the SmithKline – RIT recombinant DNA yeast-derived hepatitis B vaccine in homosexual males. |
| HBV-024 | Immunogenicity and efficacy of recombinant DNA hepatitis B vaccine in institutionalized mentally retarded – preliminary results. |
| HBV-024 | Immunogenicity and efficacy of recombinant DNA hepatitis B vaccine in institutionalized mentally retarded – final report. |

The efficacy of the *Engerix-B* vaccine has been well studied and documented.

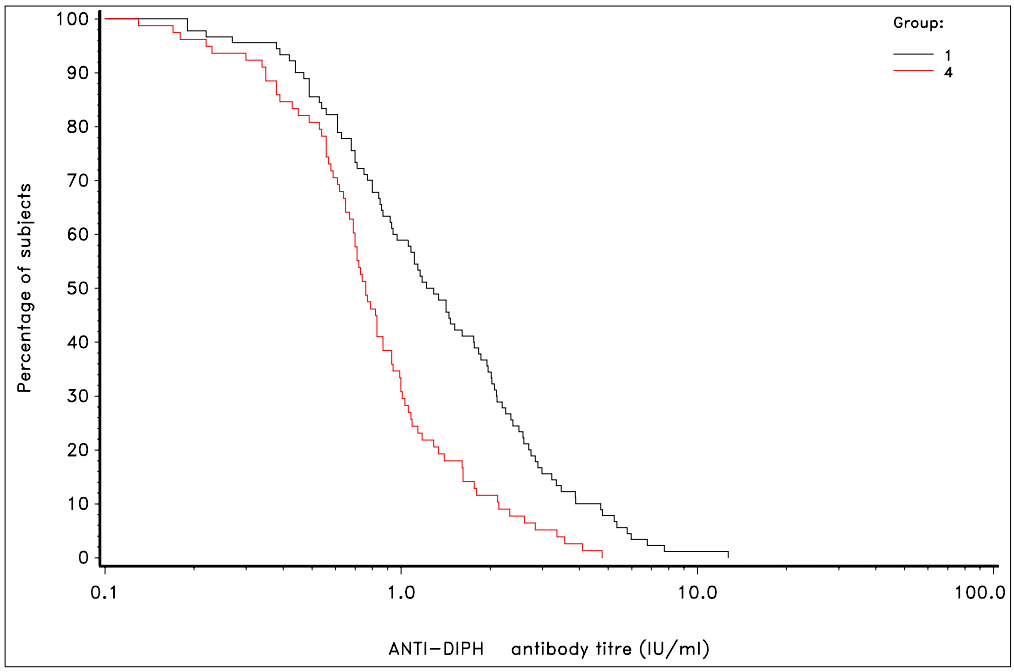
# Appendix IV

**Reverse Cumulative Curves**
**Antibody Titers for each Component of**
**DTPa-HepB-IPV**

**[Anti-DIPH, Anti-TET, Anti-HBs, Anti-PT, Anti-FHA, Anti-PRN, Anti-POLIO 1, 2, & 3 and Anti-PRP]**

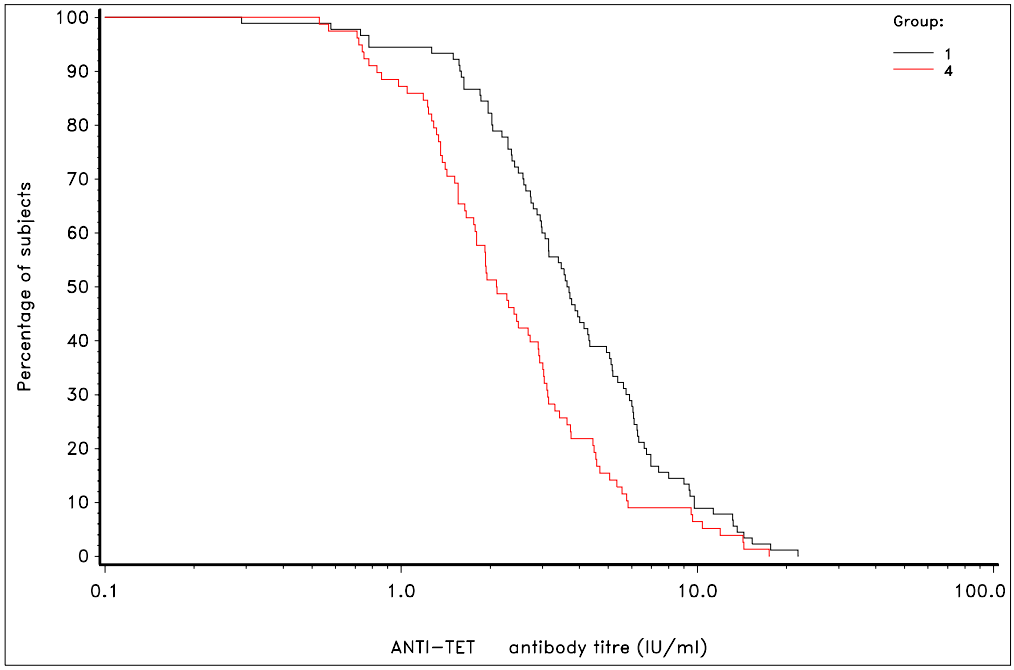
**Study DTPa-HepB-IPV-015**

**Figure 20: Reverse Cumulative Distribution Curve for anti-DIPH (post-vaccination): Subjects included in the ATP cohort for analysis of immunogenicity (Study DTPa-HepB-IPV-015)**



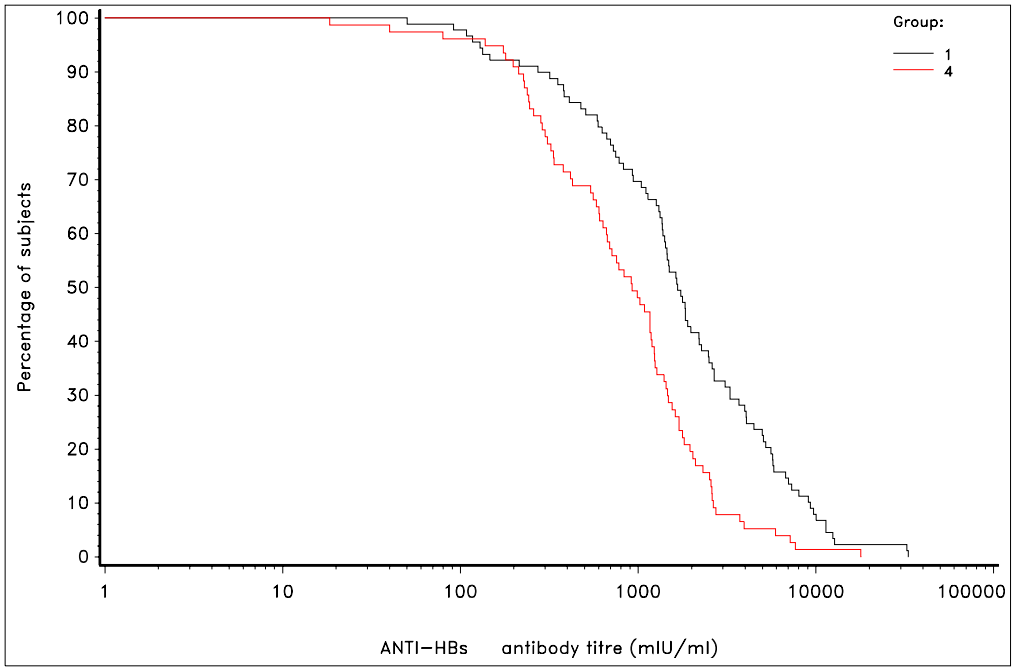

**Group 1:** DTPa-HepB-IPV + Hib
**Group 4:** DTPa + HepB + Hib + OPV

**Figure 21: Reverse Cumulative Distribution Curve for anti-TET (post-vaccination): Subjects included in the ATP cohort for analysis of immunogenicity (Study DTPa-HepB-IPV-015)**



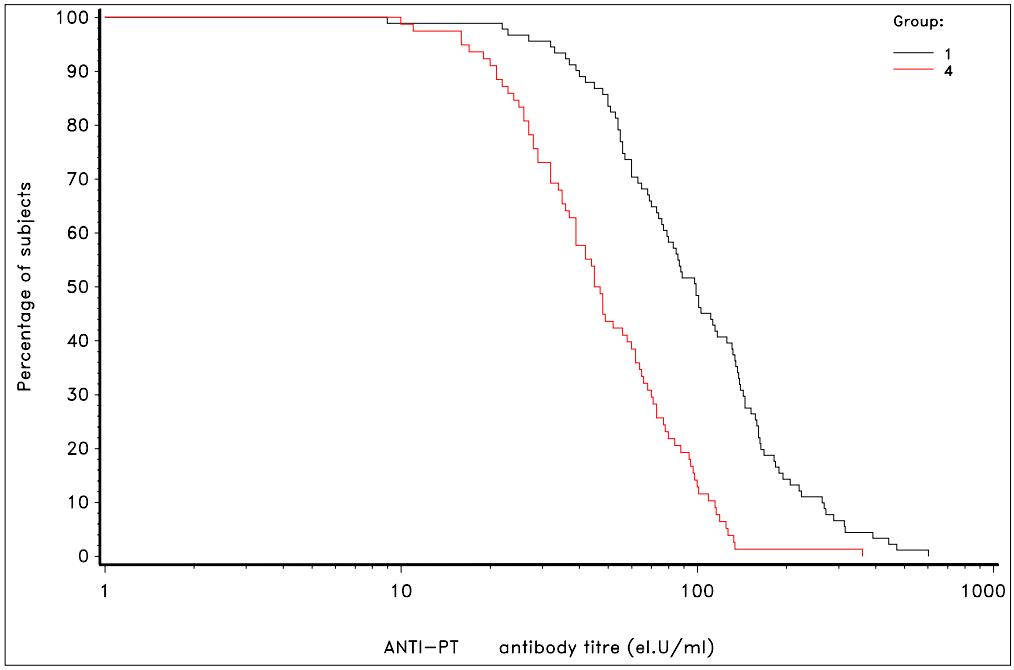

**Group 1:** DTPa-HepB-IPV + Hib
**Group 4:** DTPa + HepB + Hib + OPV

**Figure 22: Reverse Cumulative Distribution Curve for anti-HBs (post-vaccination): Subjects included in the ATP cohort for analysis of immunogenicity (Study DTPa-HepB-IPV-015)**



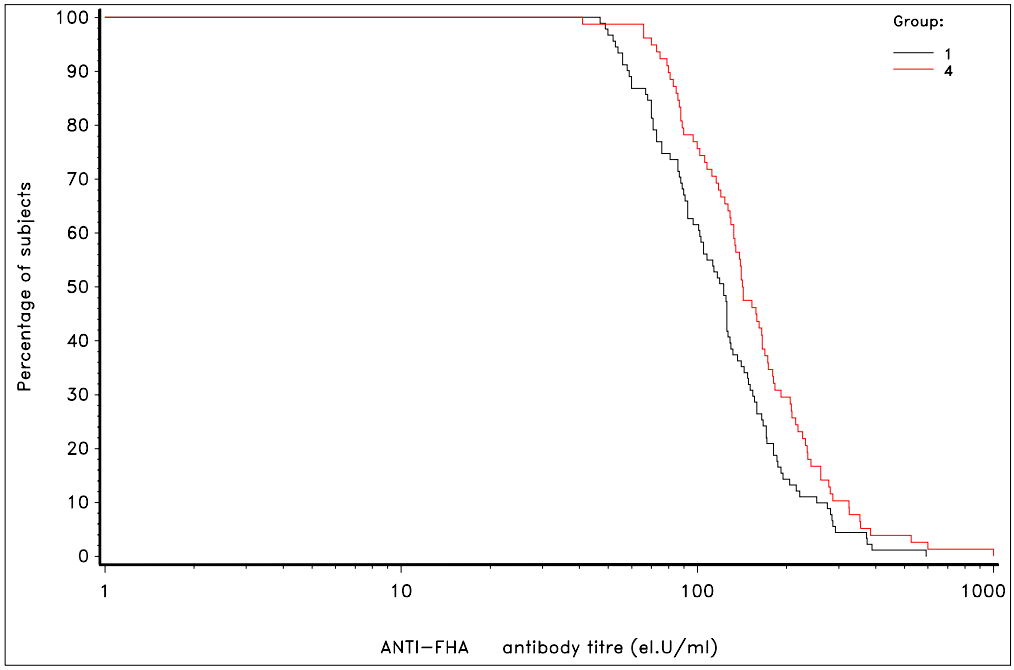

**Group 1:** DTPa-HepB-IPV + Hib
**Group 4:** DTPa + HepB + Hib + OPV

**Figure 23: Reverse Cumulative Distribution Curve for anti-PT (post-vaccination): Subjects included in the ATP cohort for analysis of immunogenicity (DTPa-HepB-IPV-015)**



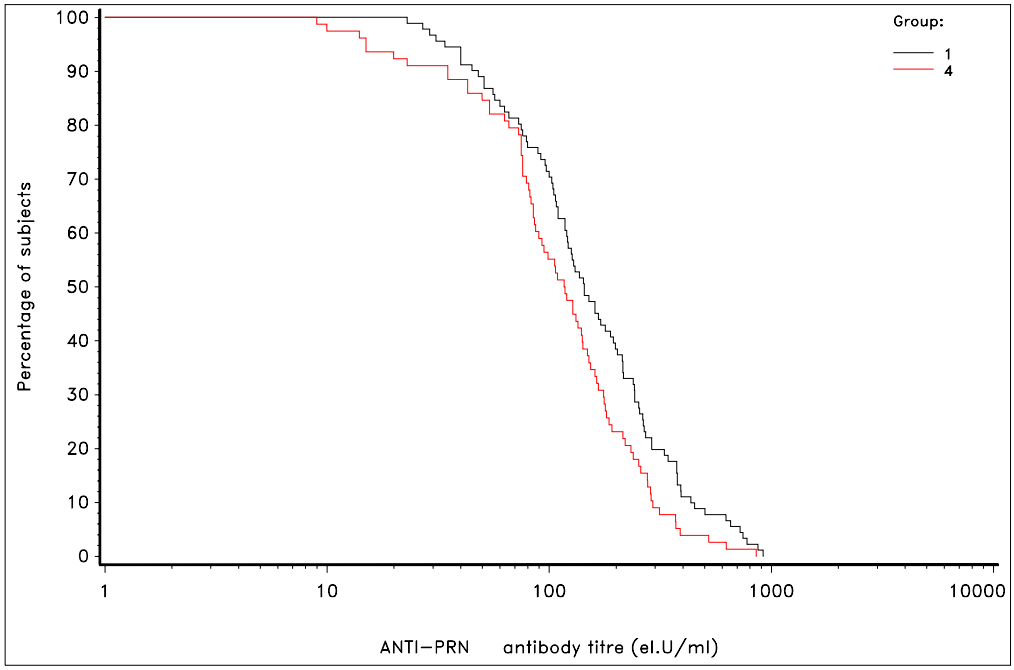

**Group 1:** DTPa-HepB-IPV + Hib
**Group 4:** DTPa + HepB + Hib + OPV

**Figure 24: Reverse Cumulative Distribution Curve for anti-FHA (post-vaccination): Subjects included in the ATP cohort for analysis of immunogenicity (DTPa-HepB-IPV-015)**



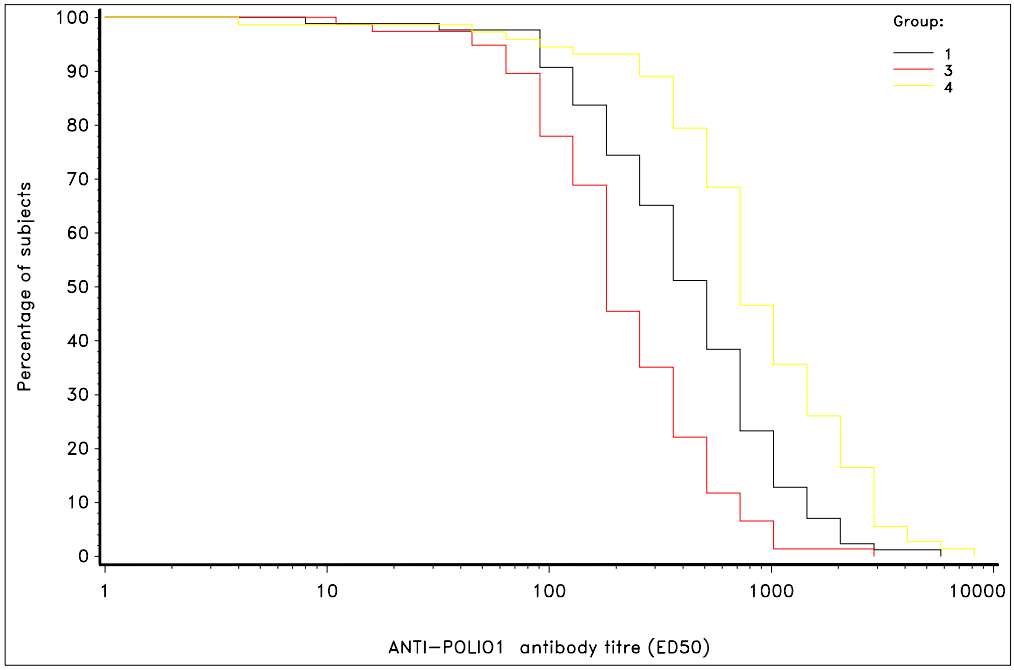

**Group 1:** DTPa-HepB-IPV + Hib
**Group 4:** DTPa + HepB + Hib + OPV

**Figure 25: Reverse Cumulative Distribution Curve for anti-PRN (post-vaccination): Subjects included in the ATP cohort for analysis of immunogenicity (Study DTPa-HepB-IPV-015)**



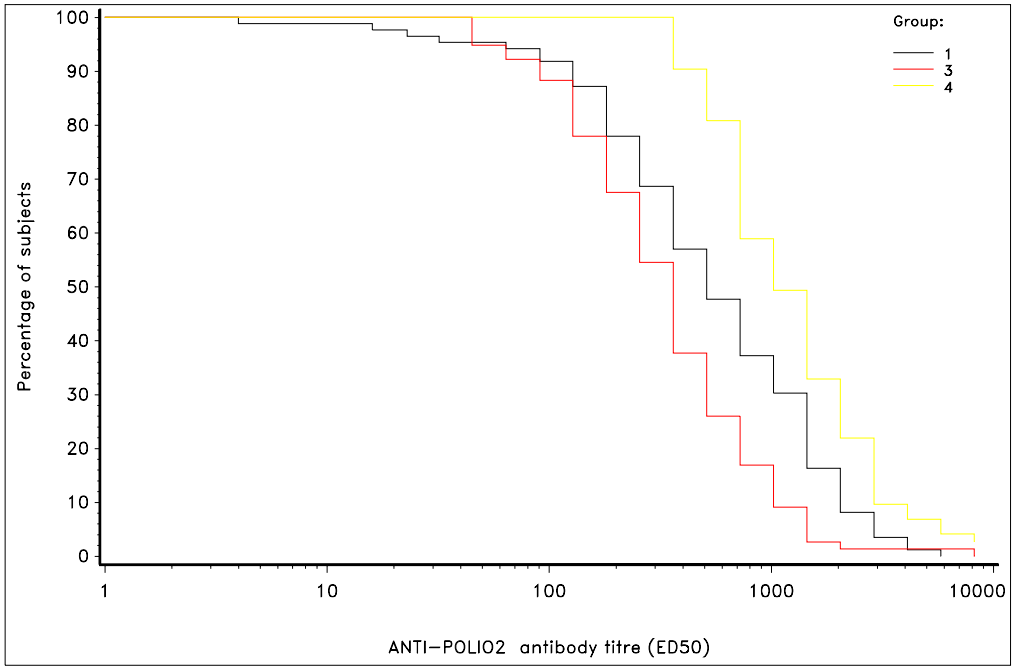

**Group 1:** DTPa-HepBVIPV + Hib
**Group 4:** DTPa + HepB + Hib + OPV

**Figure 26: Reverse Cumulative Distribution Curve for anti-POLIO1 (post-vaccination): Subjects included in the ATP cohort for analysis of immunogenicity (Study DTPa-HepB-IPV-015)**



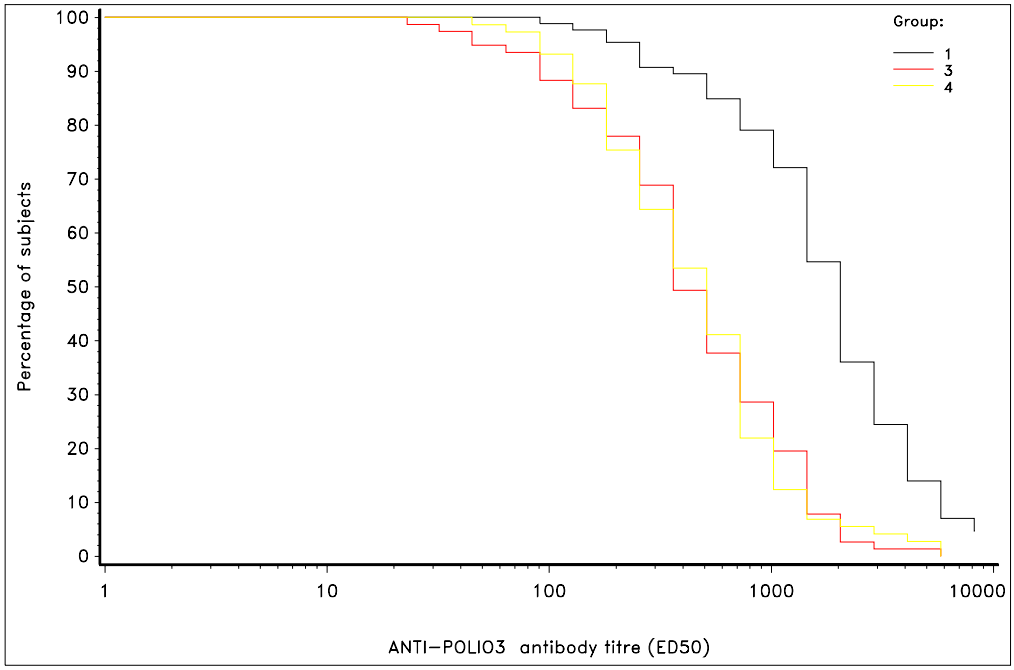

Group 1: DTPa-HepB-IPV + Hib
Group 3: DTPa-HepB + Hib + IPV
Group 4: DTPa + HepB + Hib + OPV

**Figure 27: Reverse Cumulative Distribution Curve for anti-POLIO2 (post-vaccination): Subjects included in the ATP cohort for analysis of immunogenicity (Study DTPa-HepB-IPV-015)**



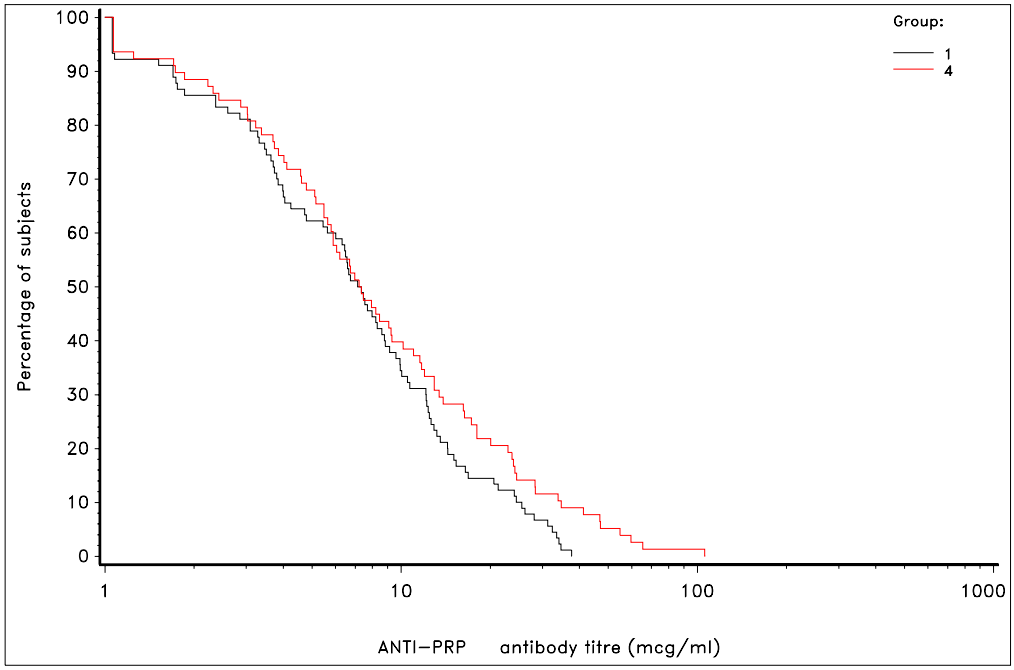

Group 1: DTPa-HepB-IPV + Hib
Group 3: DTPa-HepB + Hib + IPV
Group 4: DTPa + HepB + Hib + OPV

**Figure 28: Reverse Cumulative Distribution Curve for anti-POLIO3 (post-vaccination): Subjects included in the ATP cohort for analysis of immunogenicity (DTPa-HepB-IPV-015)**




Group 1: DTPa-HepB-IPV + Hib
Group 3: DTPa-HepB + Hib + IPV
Group 4: DTPa + HepB + Hib + OPV

**Figure 29: Reverse Cumulative Distribution Curve for anti-PRP (post-vaccination): Subjects included in the ATP cohort for analysis of immunogenicity (DTPa-HepB-IPV-015)**




**Group 1:** DTPa-HepB-IPV + Hib
**Group 4:** DTPa + HepB + Hib + OPV

# Appendix V

Equivalence testing studies:

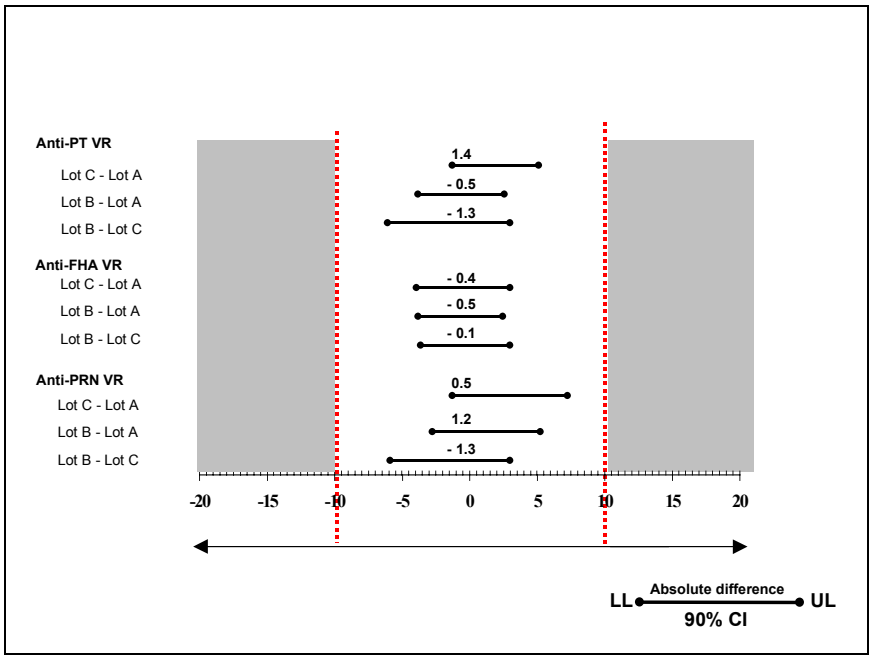
DTPa-HepB-IPV/Hib-027

&

DTPa-HepB-IPV/Hib-048

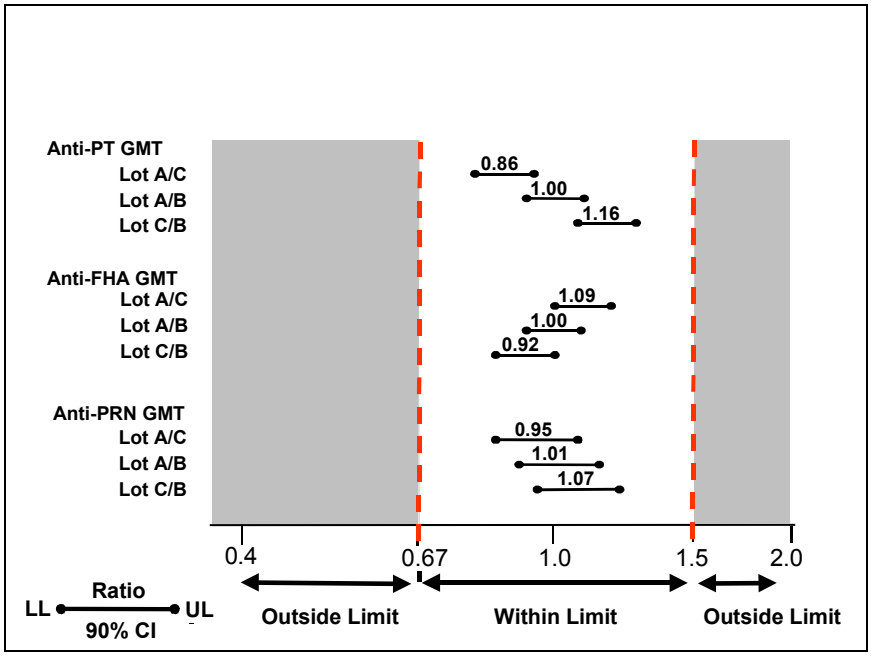
NOTE – Identical lots of DTPa-HepB-IPV were employed in these 2 studies as in study DTPa-HepB-IPV-044

**Figure 30: Equivalence testing of VR% for anit-PT, anti-FHA, and anti-PRN (Lot-to-Lot consistency) Study DTPa-HepB-IPV/Hib-027**



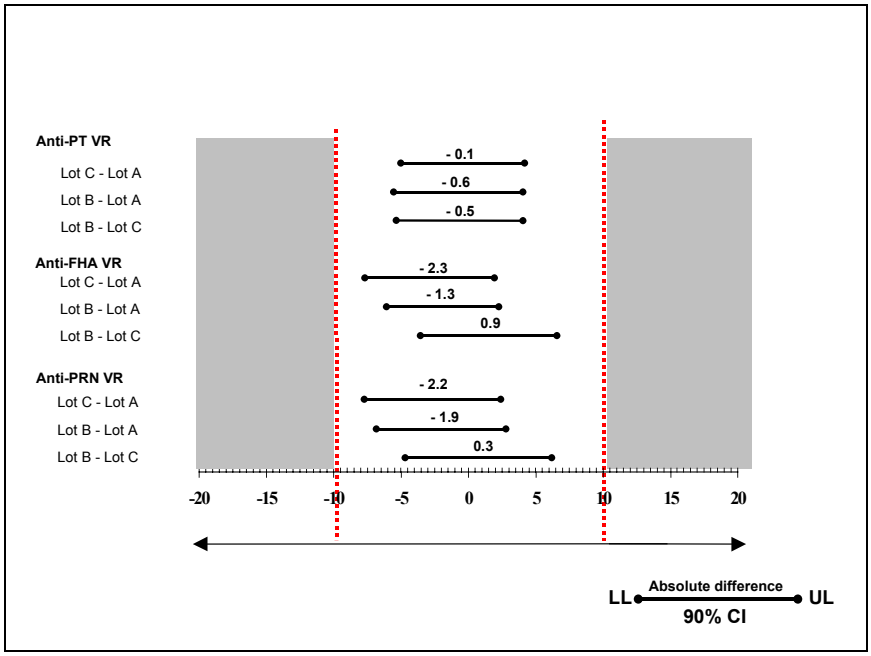

Lots A, B & C = DTPa-HepB-IPV mixed extemporaneously with Hib
Value above the bar is the point estimate of the absolute difference of Vaccine response %
90% CI = Exact 90% confidence interval; LL = Lower limit of CI; UL = Upper limit of CI
**Vaccine response definition:**
•Pertussis antibodies:
-initially seronegative subjects with post-vaccination titer cut-off (≥ 5 EL.U/mL)
-initially seropositive subjects with post-vaccination titer ≥ pre-vaccination titers

**Figure 31: Equivalence testing of GMTs for anti-PT, anti-FHA, and anti-PRN (lot-to-lot consistency) – Study DTPa-HepB-IPV/Hib-027**



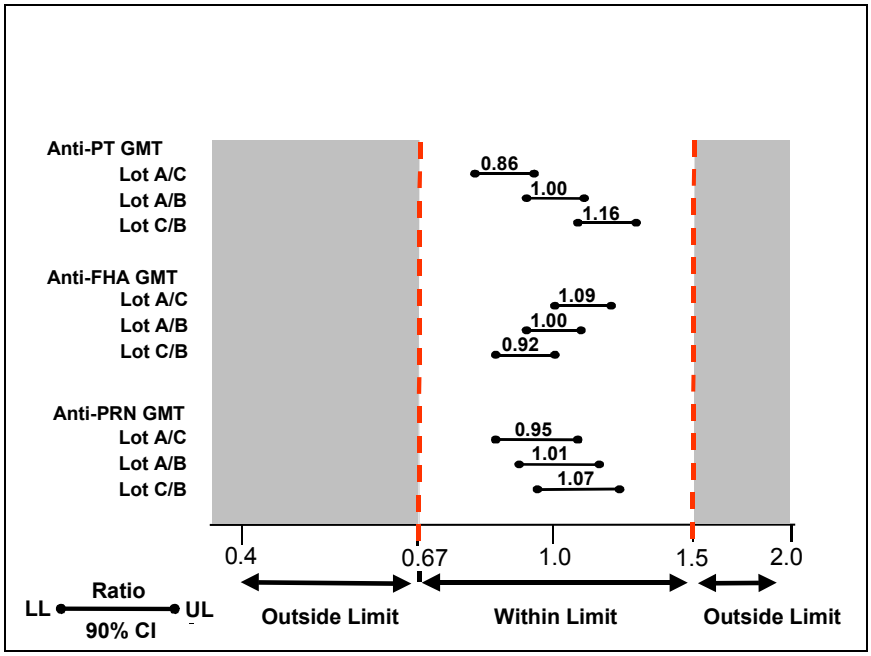

Lot A, B, and C = DTPa-HepB-IPV mixed extemporaneously with Hib
Value above the bar is the point estimate of the ratio of GMT
90% CI = 90% confidence interval; LL: Lower limit UL: Upper limit

**Figure 32: Equivalence testing of Vaccine response % for anti-PT, anti-FHA, and anti-PRN (lot-to-lot consistency) – Study DTPa-HepB-IPV/Hib-048**




Lots A, B & C = DTPa-HepB-IPV mixed extemporaneously with Hib
Value above the bar is the point estimate of the absolute difference of Vaccine response %
90% CI = Exact 90% confidence interval; LL = Lower limit of CI; UL = Upper limit of CI
**Vaccine response definition:**
•Pertussis antibodies:
-initially seronegative subjects with post-vaccination titer cut-off (≥ 5 EL.U/mL)
-initially seropositive subjects with post-vaccination titer ≥ pre-vaccination titers

**Figure 33: Equivalence testing of GMTs for anti-PT, anti-FHA, and anti-PRN (lot-to-lot consistency) – Study DTPa-HepB-IPV/Hib-048**




Lot A, B, and C = DTPa-HepB-IPV mixed extemporaneously with Hib
Value above the bar is the point estimate of the ratio of GMT
90% CI = 90% confidence interval; LL: Lower limit UL: Upper limit