Vaccines and Related Biological Products Advisory Committee

March 7, 2001

FDA Briefing Document for

SmithKline Beecham Biologicals'

DTPa-HepB-IPV Vaccine

BLA Ref. No. 99-0800
STN# 103907

Clinical Review

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1.0 Questions for the VRBPAC (DRAFT)

The questions below have been used to provide a framework for the briefing document. The finalized questions will be presented at the March meeting.

Question #1 (VOTE): The following questions pertain to efficacy:

A) Are the available data adequate to support the efficacy of DTPa-HepB-IPV vaccine when given to infants in a primary series at 2, 4, and 6 months of age?

B) If the data are not adequate to address efficacy, what additional information should be requested?

Question #2 (VOTE): The following questions pertain to safety:

A) Are the available data adequate to demonstrate the safety of the DTPa-HepB-IPV combination vaccine when given to infants in a primary series at 2, 4, and 6 months of age? Please comment on the increased rates of fever.

B) If the data are not adequate to demonstrate safety, what additional information should be requested?

Discussion Point #3:

Please discuss the data submitted in support of the concurrent administration of other routinely recommended childhood immunizations with the DTPa-HepB-IPV vaccine in infants, i.e., *Haemophilus influenzae* type b vaccine and 7-valent pneumococcal conjugate vaccine (Prevnar).

Discussion Point #4:

Please identify any issues that should be addressed in post-licensure studies. Please specifically include a discussion of the safety and immunogenicity of concurrent administration of other routinely recommended vaccines (e.g., Prevnar); safety and immunogenicity of 4th and 5th dose of Infanrix® DTPa following a primary series of DTPa-HepB-IPV; and safety of a primary series of DTPa-HepB-IPV following a birth dose of hepatitis B vaccine.

VRPBAC Briefing Document

Infanrix$_{DTPa}$ HepB-IPV™
SmithKline Beecham Biologicals (GlaxoSmithKline)*
BLA 99-0800/STN# 103907

2.0 Overview of BLA

SmithKline Beecham Biological's (SBB) DTPa-HepB-IPV vaccine is a liquid combination vaccine formulated by pooling purified bulk preparations of diphtheria and tetanus toxoids (DT); acellular pertussis (pertussis toxoid [PT], filamentous hemagglutinin [FHA], and pertactin); hepatitis B surface antigen (HBs) and inactivated poliovirus (IPV) types 1, 2, and 3. The DT toxoids adsorbed combined bulk is manufactured by Chiron-Behring GmbH and Co., Marburg, Germany. The acellular pertussis components are manufactured by SBB, Rixensart, Belgium. The combined DTPa components (Infanrix®) were approved for use in the U.S. on January 29, 1997. The hepatitis B surface antigen is similar to that found in Engerix-B® approved by the U.S. FDA on August 29, 1989. The IPV component is not licensed in the U.S.

In licensing combination vaccines the FDA is directed by the Code of Federal Regulations (CFR). A new license is required when already licensed products are combined or when unlicensed components are added to a licensed vaccine [21CFR 610.17]. In addition, safe and effective products may be combined if each component makes a contribution to the claimed effects and combining does not decrease the purity, potency, safety, or effectiveness of individual components [21CFR 601.25]. In applying the latter regulation, the FDA has relied on the concept that clinical studies of combination vaccines should be designed to rule out clinically meaningful differences, as described in the 1997 guidance document, "Guidance for Industry for the Evaluation of Combination Vaccines for Preventable Diseases: Product, Testing and Clinical Issues" (Appendix 3).

The approach to licensure of DTPa-HepB-IPV has been to demonstrate non-inferiority of the combination vaccine with respect to efficacy and safety when compared to separate administration of U.S. licensed component vaccines. As mentioned above, the DTPa and hepatitis B components of SBB's DTPa-HepB-IPV vaccine are already licensed in the U.S. as Infanrix® (Appendix 4) and Engerix-B® (Appendix 5), respectively. The IPV component is not currently licensed in the U.S. Licensure of Infanrix® and Engerix-B® was based clinical endpoint efficacy studies (see Appendices 4 and 5). Although there exists no generally accepted immunologic correlate(s) of protection against pertussis, demonstration of a comparable (non-inferior) antibody response between the acellular pertussis components of the combination vaccine to the licensed acellular pertussis vaccine of established efficacy has been used to support efficacy in this application. For antigens with identified correlates of protection (i.e., D, T, HBs, and polio types 1, 2, and 3), evidence for efficacy has been provided by demonstrating that the immune response to these antigens surpasses the level previously established as a protective response. Additional evidence for efficacy of the D, T, HBs and polio types 1, 2, and 3 components has been sought by demonstrating non-inferiority of the immune responses to the combination vaccine compared with separately administered components. However, even if the immune response to an antigen in the combination product is decreased compared to separately administered vaccines, it may still be possible to conclude that the immune response to this component in the new combination is acceptable.

The overall objective of the clinical plan for DTPa-HepB-IPV has been to demonstrate safety and immunogenicity of this vaccine when administered as a 3 dose primary series in infants. Additionally, the manufacturer has sought to demonstrate that the vaccine can be manufactured consistently and produce consistent results with respect to reactogenicity and immunogenicity. Finally, additional studies looked at the effect of concurrent administration of *Haemophilus influenzae* type b (Hib) vaccine. Of note, no data have been submitted to the FDA to date evaluating DTPa-HepB-IPV with concurrent Prevnar, Wyeth-Lederle's 7 valent pneumococcal conjugate vaccine, as this product was not licensed until after submission of the BLA.

* SmithKline Beecham Biologicals has recently merged with Glaxo. The manufacturer will be referred to as SBB in this document because the change in name is not yet official for U.S. regulatory purposes.

2.1 Proposed Indication:

Marketing authorization is sought for the following:

Indication: "Infanrix $_{DTPa}$ HepB-IPV™ is indicated for 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 series in infants and children 6 weeks to 7 years (prior to the 7th birthday)."

Dose: 0.5mL injections containing: 25 Lf diphtheria toxoid; 10 Lf tetanus toxoid; 25 µg PT; 25 µg FHA; 8 µg pertactin; 10 µg HBs; 40 D-antigen units (DU) type 1 poliovirus; 8 DU type 2 poliovirus; 32 DU type 3 poliovirus.

Schedule: three injections at 4 to 8 week intervals (2, 4, 6 months of age, customary) administered intramuscularly.

How Supplied: turbid, white suspension in single-dose (0.5mL) vials and single-dose, pre-filled, disposable syringes.

2.2 Vaccine formulation

The DTPa-HepB-IPV combination consists of the following components in each 0.5 mL dose:

Composition	Quantity (per 0.5 ml dose)
Active Substances	
Pertussis toxoid (PT), adsorbed (ads.)	25 µg
Filamentous haemagglutinin (FHA), adsorbed	25 µg
Pertactin (69kDa Outer Membrane Protein, PRN), ads.	8 µg
Diphtheria toxoid (D), ads.	≥ 2 U/ml or 25 Lf
Tetanus toxoid (T), ads.	≥ 2 U/ml or 10 Lf
r-DNA Hepatitis B surface antigen, ads.	10 µg (HBs)
Inactivated Poliovirus Type 1	40 DU
Inactivated Poliovirus Type 2	8 DU
Inactivated Poliovirus Type 3	32 DU
Excipients	
2-phenoxyethanol	2.5 mg
Sodium Chloride	4.5 mg
Water for Injection	0.5 ml
Adjuvants	
Aluminum salts (Aluminum hydroxide 0.5 mg and aluminum phosphate 0.2 mg)	0.7 mg

The diphtheria and tetanus toxoids, adsorbed combined bulk are produced by Chiron Behring, GmbH and Co., Marburg, Germany. The acellular pertussis antigens, hepatitis B surface antigen, and trivalent inactivated polio virus vaccine are produced by SmithKline Beecham Biologicals (SBB). SBB performs the formulation, filling, testing, packaging and release of the final product.

2.3 Manufacturing Changes During Development of DTPa-HepB-IPV: See FDA's Confidential Briefing Document

2.4 Abbreviated U.S. Regulatory Timeline

02/29/96	Original Submission IND 6542: Safety and immunogenicity "equivalence" study (DTPaHepB-IPV-015, U.S.)
06/25/96	Letter to Sponsor (Advice/IR)
07/19/96	6542/5, Submission of large scale safety trial (DTPa-HepB-IPV-011, Germany)
06/12/97	IPV Meeting with Sponsor
12/02/97	Pre-phase 3 Meeting with Sponsor: • Manufacturing Issues: Process Modifications • Clinical Issues: Discussion of pivotal studies
01/27/98	6542/20 – Submission of revised lot consistency/bridging study (DTPa-HepB-IPV-044U.S.)
10/28/98	End of Phase III/Pre-Biologics License Application (BLA) Meeting
02/23/99	Pre-BLA Meeting
07/02/99	BLA submission
09/99	Pre-Approval Inspection
02/09/00	FDA Information Request Letter
05/01/00	FDA Complete Response Letter
12/18/00	Submission of Complete Response

3.0 Clinical Studies

3.1 Overview of Clinical Studies

3.1.1 Objectives of Clinical Studies

1. Establish the safety of DTPa-HepB-IPV
   - To rule out important differences in the safety and reactogenicity of the combination vaccine compared to separately administered components.
2. Establish the efficacy of DTPa-HepB-IPV
   - Efficacy to be established via immunogenicity of each component in the combination.
   - Rule out important differences between the immune response to each antigen elicited by DTPa-HepB-IPV compared to the separately administered components.
3. Establish the safety and efficacy with concurrent immunizations
   - Evaluate immunogenicity of DTPa-HepB-IPV when administered concurrently with routinely recommended U.S. licensed vaccines anticipated to be given on the same schedule (i.e., *Haemophilus influenzae* type b).
4. Demonstrate clinical consistency of production lots of DTPa-HepB-IPV.
5. Demonstrate clinical bridging (comparative immunogenicity) between two sequential series of production lots following a manufacturing change.
6. Compare the immunogenicity of the hepatitis B surface antigen (HBs) when given in the combination at 2, 4, and 6 months of age versus the U.S. licensed regimen for hepatitis B (Engerix B) vaccination of 0, 1 and 6 months.

3.1.2 Pivotal Trial Summary

Three clinical trials, **Study DTPa-HBV-IPV-011 (011), Study DTPa-HBV-IPV-015 (-015), and Study DTPa-HBV-IPV-044 (-044)**, were submitted as pivotal studies in support of the requested indication for DTPa-HepB-IPV as a three dose primary series. Because the DTPa and hepatitis B components of this vaccine are already licensed in the US (as Infanrix® and Engerix-B®, respectively), and generally accepted correlates of immunity exist for the IPV component, evidence of efficacy was based on demonstrating non-inferiority of DTPa-HepB-IPV with respect to immunogenicity of each component compared to separate administration of U.S. licensed component vaccines

(Infanrix®, Engerix-B®, and oral or inactivated polio vaccines [OPV or IPV]). Immunogenicity data were obtained from Studies -015 and -044; safety data were obtained from all three pivotal studies. Safety of concurrent immunization with Hib vaccine was studied in all three pivotal studies and immunogenicity of concurrent Hib was studied in -015 and -044. Data on concurrent administration of Prevnar, Wyeth Lederle's 7-valent pneumococcal conjugate vaccine licensed in February 2000, were not part of the DTPa-HepB-IPV BLA (submitted in July 1999).

Study DTPa-HepB-IPV- 011,a large scale comparative safety trial of DTPa-HepB-IPV was conducted in Germany under a 3, 4, 5 month primary immunization schedule with concurrent *Haemophilus influenzae* type b (Hib) vaccine. This trial was amended after initiation to expand enrollment and include a control group receiving separately administered U.S. licensed vaccines, i.e., DTPa, OPV, and Hib. The separate administration control group did not receive hepatitis B vaccine during the study period.

Study DTPa-HepB-IPV-015, conducted in the U.S. under a 2, 4, and 6 month primary schedule, compared the safety and immunogenicity of 3-dose primary series of DTPa-HepB-IPV and Hib with either a sequential IPV/OPV schedule or separately administered U.S. licensed vaccines, e.g., DTPa, hepatitis B, OPV and Hib.

Study DTPa-HepB-IPV-044, conducted in the U.S. under a 2, 4, 6 month schedule, evaluated lot consistency and manufacturing bridge from the 1st to the 2nd lot series. Hib was administered concurrently in each group.

3.1.3 Inclusion/Exclusion Criteria for Pivotal Studies

In general, criteria for inclusion were consistent across pivotal studies with minor differences. Study DTPa-HepB-IPV-011 enrolled subjects who were 8-16 weeks of age while Studies –015 and –044 enrolled subjects who were 6-12 weeks of age at study entry. Study DTPa-HepB-IPV-011 did not exclude subjects born following a preterm (< 36 week) gestation; Studies -015 and -044 excluded former preterm infants. On entry (all pivotal studies) subjects were to be free of obvious health problems, and born to mothers seronegative for HBsAg. Subjects were excluded if they had a known hypersensitivity to any vaccine component, had previously received any vaccines or any blood or blood product (including Hepatitis B Immune Globulin), were born to mothers known to be HIV positive, had temperatures $\geq$ 38ºC (100.4°F) rectally at first study visit. In addition, Study –044 specifically excluded subjects with acute disease at the time of enrollment, defined as "presence of a moderate or severe illness with or without fever." In Study-044, vaccines could be administered to persons with minor illness such as diarrhea or mild-upper respiratory infection with or without low-grade febrile illness.

Pivotal Trial Summary

Study/ Location	Objectives	Endpoints	Schedule (mo)	Concurrent vaccines	N receiving DTPa-HepB-IPV*	N in Control Group (Separately Administered Vaccines)*
011 Germany	Large scale comparative safety vs separate vaccines	Safety only	3, 4, 5	Hib	4695	776**
015 USA	Comparative vs separate vaccines (U.S. schedule)	Safety and immunogenicity	2, 4, 6	Hib	200	200
044 USA	Lot consistency; Manufacturing bridge from 1st to 2nd lot series	Safety and immunogenicity	2, 4, 6	Hib	484	§

*Total cohort (number enrolled)

** Study-011 was amended after initial enrollment to include a control group receiving separately administered US licensed vaccines.

§There was no control group receiving separately administered vaccines in Study-044.

Study Designs: DTPa-HepB-IPV-011, DTPa-HepB-IPV-015, and DTPa-HepB-IPV-044 (adapted from BLA Table 8.II.9- 1)

DTPa-HepB-IPV-011		DTPa-HepB-IPV-015		DTPa-HepB-IPV-044	
Country	Germany	**Country**	USA	**Country**	USA
Schedule	3, 4, 5 months of age	**Schedule**	2, 4, 6 months of age	**Schedule**	2, 4, 6 months of age
Groups 1 - 4 pooled	DTPa-HepB-IPV + Various Hib*	**Group 1**	DTPa-HepB-IPV + PM Hib	**Group 1**	DTPa-HepB-IPV (Lot A 2nd lot series)+ PM Hib
		Group 2	DTPa-HepB-IPV + Hib (2, 4 months)	**Group 2**	DTPa-HepB-IPV (Lot B 2nd lot series) + PM Hib
			DTPa-HepB + PM Hib + Lederle OPV (6 months)	**Group 3**	DTPa-HepB-IPV (Lot C 2nd lot series) + PM Hib
		Group 3	DTPa-HepB + PM IPV + PM Hib		
Group 5	SBB DTPa + PM Hib + Lederle OPV	**Group 4**	SBB DTPa + SBB HepB + PM Hib + Lederle OPV	**Group 4**	DTPa-HepB-IPV (1st lot series) + PM Hib

*Group 1 = SBB Hib; Group 2 = Pasteur Merieux Connaught (PM-now Aventis Pasteur) Hib; Group 3 = Lederle Hib; Group 4 = Merck Hib

3.1.4 Supportive Studies

Primary series

In addition to the pivotal trials, safety and immunogenicity data from additional studies were submitted in support of the BLA. These included 1) additional studies of DTPa-HepB-IPV not conducted under US IND; and 2) studies of other Infanrix®-based combination vaccines providing supportive data on safety and immunogenicity. The latter category included Study DTPa-HepB-030 which provided immunogenicity data from SBB's DTPa-HepB combination to support the change in hepatitis B vaccination schedule from 0, 1, and 6 months (Engerix-B®) to the 2, 4, 6 months schedule of DTPa-HepB-IPV. In addition, supportive data on safety of a primary series of DTPa-HepB-IPV following a birth dose of hepatitis B vaccine was submitted in the form of Study DTPa-HepB-IPV-030 and Study DTPa-HepB-IPV/Hib-003. DTPa-HepB-IPV/Hib-003 provided data on SBB's DTPa-HepB-IPV mixed extemporaneously prior to injection with SBB's PRP-T vaccine (not licensed in the U.S.)

DTPa Booster

The license application for DTPa-HepB-IPV requests an indication for primary series immunization. Overall clinical development of DTPa-HepB-IPV included studies evaluating a toddler booster of DTPa (Infanrix®) or a fourth consecutive dose of DTPa-HepB-IPV following a primary series of DTPa-HepB-IPV. While not formally considered under this BLA, SBB has submitted summary safety and immunogenicity data on 4th (toddler) dose of Infanrix® or Infanrix®-based combinations following a primary series with DTPa-HepB-IPV. (See Section 3.5 and Appendix 2 of this review.)

3.1.5 Clinical Trial Summary (Pivotal + Supportive)

Study Number	Vaccine (Lot Series)	Objective	Country	Study Arms: DTaP-HepB-IPV vs Comparator	N = receiving DTPa-HepB-IPV#	N= Compar.	Sched-ule (mo)	Comment
001 (Pilot)	DTPa-HepB-IPV (1st Lot)	Feasibility	Turkey	DTaP-HepB-IPV vs DTPa-HepB+IPV	20	20	3, 4, 5	Research lot
002 (Pilot)	DTPa-HepB-IPV (1st Lot)	Feasibility	Finland	DTaP-HepB-IPV	30	0	2, 4, 6	
004 (Pilot)	DTPa-HepB-IPV (1st Lot)	Feasibility	Canada	DTaP-HepB-IPV	50	0	2, 4, 6	
005 (Supportive)	DTPa-HepB-IPV (1st Lot)	Lot consistency	Belgium	DTaP-HepB-IPV (3 consistency lots)	567	0	3, 4, 5	
011 (Pivotal)	**DTPa-HepB-IPV (1st Lot)**	**Large scale safety**	**Germany**	**DTaP-HepB-IPV+SBB Hib (1) vs DTaP-HepB-IPV +PMC Hib (2) vs DTaP-HepB-IPV +Led Hib (3) vs DTaP-HepB-IPV +Merck Hib (4) vs. DTPa+Hib+OPV (5)**	**4695 (Groups 1-4)**	**776 (Group 5)**	**3, 4, 5**	**-Original objective to compare different Hib formulations -Amended to compare to US licensed separate injections -No serology performed -Not on US schedule of 2, 4, 6 months**
012 (Supportive)	DTPa-HepB-IPV (1st Lot)	Hib co-administration	Lithuania	DTaP-HepB-IPV+SBB Hib vs DTaP-HepB-IPV +PMC Hib vs DTaP-HepB-IPV +Led Hib vs DTaP-HepB-IPV +Merck Hib	549	0	3, 4.5, 6	
015 (Pivotal)	**DTPa-HepB-IPV (1st Lot)**	**1) Comparative immunogenicity vs separate injections 2) Safety (common AEs) 3)Simultaneous imm. (Hib)**	**USA**	**DTPa-HepB-IPV+Hib @2,4, 6 mo (Group 1) vs DTPa-HepB-IPV+Hib @2,4, and DTPa-HepB+OPV+Hib @6mo (Group 2) vs DTPa-HepB +IPV+ Hib (Group 3) vs DTPa + HepB+OPV+ Hib (Grp 4)**	**200**	**200**	**2, 4, 6**	
016 (Supportive)	**DTPa-HepB-IPV (1st Lot)**	1)Safety 2)Immunogenicity	Germany	DTPa-HepB-IPV/Hib vs DTPa-IPV/Hib+HepB	184	368	3, 4, 5	

Manufacturer abbreviation: SBB=SmithKline Beecham Biologicals; PMC=Pasteur Merieux Connaught, now known as Aventis Pasteur; Led=Wyeth Lederle

Clinical Trial Summary (Pivotal + Supportive – cont.)

Study Number	Vaccine /Lot Series	Objective	Country	Study Arms: DTaP-HepB-IPV vs Comparator	N = receiving DTPa-HepB-IPV#	N= Compar	Sched-ule (mo)	Comment
017 (Supportive)	DTPa-HepB-IPV (1st Lot)	1)Safety 2)Immunogenicity	France	DTaP-HepB-IPV+Hib vs DTPa-HepB-IPV/Hib vs DTPa-IPV/Hib+HepB	29	180	2, 3, 4	
019 (Supportive)	DTPa-HepB-IPV (1st Lot)	1)Safety 2)Immunogenicity	Estonia	DTaP-HepB-IPV vs DTPa-HepB +IPV	60	60	3,4.5,6	
030 (Supportive)	DTPa-HepB-IPV (2nd Lot)	Safety after birth dose HepB	Moldova	birth dose HepB+ DTPa-HepB-IPV @ 6, 10, 14 wks vs birth dose HepB+DTPw-IPV-Hib +HepB @ 6, 10, 14 weeks	160	160	6,10,14 weeks	-All infants received birth dose of hepB -Compressed schedule (6, 10, 14 wks) -Comparator includes whole cell pertussis vaccine
044 (Pivotal)	**DTPa-HepB-IPV (1st Lot) and DTPa-HepB-IPV (2nd Lot)**	**1)Lot consistency 2)Bridge from 1st lot to 2nd lot for safety and immunogenicity**	**USA**	**DTPa-HepB-IPV (Groups 1-3) (3 lots of 2nd lot series) vs DTPa-HepB-IPV (Group 4) (1 lot of 1st lot series)**	**484 1:1:1:1**	**0**	**2, 4, 6**	**No separate injection control arm**
DTPa-HepB-IPV/Hiv-027 (Supportive)	*DTPa-HepB-IPV/Hib*	*Lot consistency (Safety and immunogenicity)*	*USA*	*DTPa+HepB+OPV+Hib (Group 1) vs DTPa-HepB-IPV/Hib (3 lots of DTPa-HepB-IPV 2nd lot series, same lots as -044) (Groups 2-4)*	*1085*	*358*	*2, 4, 6*	***Note: Study evaluated DTPa-HepB-IPV/Hib***
DTPa-HepB - 030 (Supportive)	*DTPa-HepB*	*Support schedule change HepB*	*USA*	*DTaP-HepB + Hib + OPV @2, 4, 6 mo vs DTaP + Hib +OPV @2,4,6 mo HepB @0, 1, 6 mo*	*N.A.*	*N.A.*	*2, 4, 6*	***Note: Study evaluated DTaP-HepB***
DTPa-HepB-IPV/HIB-003 (Supportive)	*DTPa-HepB-IPV/Hib*	*Safety after birth dose HepB*	*USA*	*DTPa-HepB-IPV/Hib (no birth dose HepB) (Group 1) vs DTPa-HepB-IPV + birth dose HepB (Group 2)*	*N.A.*	*N.A.*	*2,4,6*	***Note: Study evaluated DTPa-HepB-IPV/Hib***

Total Cohort Safety	**all studies** **Studies 011+015+044**	**Pivotal + Supportive** **Pivotal**	**7028** **5379**	**1764**
Immunogen -icity	**Studies 015+044**	**Pivotal**	**684**	

#Numbers from Electronic Submission BLA 99-0800 Item 8.1.1 Summary of Studies Table 8.I.6-1

3.2 Efficacy Data (Immunogenicity)

3.2.1 Characterization of the Immune Response: Clinical Serology

All assays were performed blinded to vaccination status. Assays were conducted in either of two laboratories: SBB Laboratories in Rixensart, Belgium or in the labs of Dr. Michael Pichichero (MEP) at the University of Rochester. Data to support the comparability of the procedures employed and the results obtained from the two laboratories were reported in the BLA.

Antigen	Serological Method	Endpoints**
DTPa-HepB-IPV antigens		
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 (HBs)	RIA	10 mIU/mL
Poliovirus types 1, 2, 3 (IPV)	Cell culture neutralization	1/8
Concurrent administration		
Haemophilus influenzae type b (Hib)	ELISA*	0.15 and 1.0 mcg/mL

*****In studies DTPa-HepB-IPV-002, 004, -005, and -012, anti-PRP antibodies were measured using radiolabeled antigen-binding assay (RABA).

******"For D, T, HBs, "seroprotection" rates (i.e., the % of infants with antibody titers equal or above the assay cut-off) were set such that subjects who had titers above the cut off could be considered protected from disease.
For polio types 1, 3, and 3, subjects with detectable neutralizing antibody were considered protected from disease.
For pertussis antigens, "vaccine response" rates (i.e., the % of infants showing a vaccine response to each pertussis antigen (PT, FHA and PRN) was defined as antibody titers equal to or above the assay cut-off in subjects who were seronegative prior to vaccination and at least maintenance of prevaccination antibody titers in those who were seropositive prior to vaccination.

3.2.2 Assessment of Immunogenicity

Subjects evaluated for immunogenicity had serum samples for measurement of antibody response obtained before vaccination and approximately one month after the third vaccine dose.

Study cohorts for immunogenicity:

Intent-to-treat (ITT) cohort for analysis of immunogenicity: All subjects enrolled in the study for whom assay results were available for antibodies against at least one study antigen either pre- or post-vaccination.

According-to-Protocol (ATP) cohort for analysis of immunogenicity:
Studies DTPa-HepB-IPV-016, -030, and -044: All evaluable subjects (i.e, those meeting all inclusion/exclusion criteria and complying with the procedures defined in the protocol, and fulfilling requirements for analysis) for whom assay results were available for antibodies against at least one study vaccine antigen post-vaccination.

All other studies: same criteria as above but must have assay results available for antibodies against at least one study antigen both pre- and post-vaccination.

Criteria for evaluation of immunogenicity:

Primary endpoints for immunogenicity were defined as seroprotection rates for D, T, HBsAg, and poliovirus (Types 1, 2, 3) and in terms of vaccine response rates and GMTs for the pertussis components (PT, FHA, and PRN). Seroprotection rates for PRP, seropositivity rates for PT, FHA and PRN, and GMTs for D, T, HBsAg, poliovirus (Types 1, 2, 3) and PRP were considered secondary endpoints.

Endpoints:

The following immunogenicity endpoints were evaluated.

- **"**Seroprotection" rates: i.e., the % of infants with antibody titers equal to or above the assay cut-off. D, T, HepB, Polio, Hib
  - D, T, hepatitis B: % infants with antibody titers ≥ the predefined levels (see table below)
  - Polio types 1, 2, 3 : % infants with neutralizing antibodies ≥ 1:8
  - Hib: % infants with anti-PRP antibodies ≥ 0.15 and 1.0 mcg/mL
- Vaccine response rates: Pertussis
  - % infants showing response to PT, FHA, PRN
  - Defined as: ≥ 5 EL.U/mL in subjects who were seronegative prior to vaccination or at least maintenance of pre-vaccination antibody titers in those "seropositive" prior to vaccination
- Geometric mean antibody titers (GMTs): The anti-log of the mean of the log titer transformation.
- Distribution of antibody responses by reverse cumulative distribution curves (RCD curves)

Statistical methodology: (From BLA 8.III.1.3)

The statistical methodology used to evaluate the immunogenicity of the study vaccine evolved during clinical development, from testing of the null hypothesis of no vaccination difference 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).

Three statistical approaches were used:

1. Descriptive analyses within each vaccine group: all studies

For each treatment group, seroprotection rates and GMTs were calculated with their 95% confidence intervals (CI) for all time points for which serum was titrated. Vaccine response rates and their 95% CI were also tabulated by treatment group.

Antibody titer distributions, approximately one month after the vaccination course, were displayed by means of reverse cumulative distribution curves.

2. Hypothesis testing of no difference between the SBB DTPa-HepB-IPV vaccine and control, or for lot-to-lot consistency (studies DTPa-HepB-IPV-005, -012).

Seroprotection/ vaccine response rates were compared between vaccine groups using Fisher's Exact test, whereas GMTs were compared using one-way ANOVA test. P-values less than 0.05 (two-sided test of the null hypothesis of no difference) were considered as indicative of statistical significance.

3. Equivalence testing between the SBB DTPa-HepB-IPV vaccine and commercial control or for lot-to-lot consistency (studies DTPa-HepB-IPV-015, -016,-030, -044, and -005 *[a posteriori* analysis]).

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 as follows:

Specified limits for non-inferiority of DTPa-HepB-IPV* relative to a control and consistency between lots of the SBB DTPa-HepB-IPV vaccine (8.III.1.3.2)

Seroprotection/vaccine response rate	**Max difference**
% subjects with anti D≥0.1 IU/mL	10%
% subjects with anti T≥0.1 IU/mL	10%
% subjects with anti-PT vaccine response	10%
% subjects with anti-FHA vaccine response	10%
% subjects with anti-PRN vaccine response	10%
% subjects with anti-HBS≥ 10 mIU/ml	10%
% subjects with anti-polio 1 ≥ 1:8	10%
% subjects with anti-polio 2 ≥ 1:8	10%
% subjects with anti-polio 3 ≥ 1:8	10%
Geometric Mean Titers (GMTs)	**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 vaccine difference was below the specified clinical limit of non-inferiority (one-sided equivalence test; alpha = 5%).

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 between vaccines (lots) was included in the specified clinical limits of equivalence (two-sided equivalence test; alpha =5%).

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. The robustness of the GMT analysis with respect to the parametric assumptions was evaluated using a Cox regression model. Both ANOVA and Cox models included the group effect as the only regressor.

3.2.3 Pivotal Study for Immunogenicity: DTPa-HepB-IPV-015 (Comparative Immunogenicity vs. Separately Administered U.S. Licensed Vaccines)

Title: An open study of the safety and immunogenicity of DTPa-HepB-IPV vaccine administered as a three dose series or in a sequential IPV/OPV schedule at 2, 4, and 6 months of age.

Objectives:

Primary Objective: To evaluate the immune response and potential interactions to each of the 10 antigens (D, T, PT, FHA, Pertactin, PRP, Hepatitis B, and polio virus types 1, 2, and 3) in infants who receive three doses of DTPa-HepB-IPV vaccine and Hib (OmniHIB™) simultaneously at separate sites compared to DTPa-HepB (SBB) administered with IPV (IPOL®) and Hib (OmniHIB™) simultaneously at separate injection sites and compared to DTPa (Infanrix®), Hepatitis B (Engerix-B®) and Hib (OmniHIB™) vaccines simultaneously at separate sites along with OPV (ORIMUNE™).

Secondary objective: To evaluate the safety and immunogenicity of the IPV component of the DTPa-HepB-IPV administered as a single injection relative to the safety and immunogenicity of OPV (ORIMUNE®) or IPV (IPOL®) administered separately along with DTPa (Infanrix®) Hepatitis B (Engerix-B®), Hib (OmniHIB™ or DTPa-HepB (SBB) and Hib (OmniHIB™). Note SBB-s DTPa-HepB vaccine is not licensed in the U.S.

To compare the safety and immunogenicity of the sequential administration of DTPa-HepB-IPV vaccine at 2 and 4 months followed by OPV (ORIMUNE®) at 6 months of age with a three dose series of DTPa-HepB-IPV vaccine.

Design: Open, randomized

Schedule: 2, 4, 6 months

Group 1: DTPa-HepB-IPV + Hib at 2, 4, 6 mo
Group 2: DTPa-HepB-IPV at 2, 4 mo; DTPa-HepB + Hib + OPV at 6 months
Group 3: DTPa-HepB + Hib + IPV at 2, 4, 6 mo
Group 4: DTPa + HepB + OPV + Hib at 2, 4, 6 mo

Number of subjects

Total enrolled (ITT cohort): 400 (100 per group)
Completed: 347

ATP for safety cohort: 399
ATP immunogenicity cohort: 332

Data analysis

As defined by SBB, the primary objective was demonstrated if the upper limits of all the 90% CIs for the difference in the primary endpoints (see section 3.3.2: specified limits of non-inferiority) between Group 1 and Group 4, were below the limit defining clinical non-inferiority.

In the review of DTPa-HepB-IPV, Group 1 (DTPa-HepB-IPV + Hib at 2, 4, and 6 months of age) and Group 4 (DTPa + HepB + Hib + OPV at 2, 4, and 6 months of age) considered. Group 2 included the sequential IPV/OPV schedule which is no longer part of the U.S. Recommended Childhood Immunization Schedule, and Group 3 evaluated SBB's DTPa-HepB combination (unlicensed in the U.S). Therefore, data presented below concentrate on groups 1 and 4.

DTPa-HepB-IPV-015: Comparison of the immunogenicity of DTPa-HepB-IPV and U.S. licensed vaccines administered separately, i.e., Group 1 vs Group 4 (ATP cohort for immunogenicity)

Antigens		Seroprotection/Vaccine Response‡							GMTs§				
		Group 1		Group 4		Difference (Group 4 minus Group 1)			Group 1	Group 4	Group 4 Divided by Group 1		
		N	%	N	%		90% CI					90% CI	
							LL	UL				LL	UL
Diphtheria		90	98.9	78	100	1.1	-5.2	8.2*	1.294**	0.805	0.62	0.50	0.77
Tetanus		90	100	78	100	0.0	-7.0	5.5*	3.730**	2.345	0.63	0.51	0.77
Hepatitis B		89	100	77	100	0.0	-7.1	5.5*	1661.2	804.9	0.48	0.35	0.67*
PT		91	98.9	78	98.7	-0.2	-8.1	6.2*	97.1	47.5	0.49	0.41	0.58*
FHA		**91**	**95.6**	**77**	**100**	**4.4**	**-2.6**	**12.8**	119.1	153.2	1.29	1.12	1.48*
PRN		91	95.6	78	91.0	-4.6	-15.0	4.3*	150.4	108.6	0.72	0.58	0.90*
Polio 1		86	100	73	98.6	-1.4	-9.7	4.7*	415.3**	819.2	1.97	1.48	2.63
Polio 2		86	98.8	73	100	1.2	-5.6	8.6*	514.2**	1261.8	2.45	1.83	3.29
Polio 3		86	100	73	100	0.0	-7.4	5.7*	1729.2**	452.6	0.26	0.20	0.34
PRP**	≥1.0 mcg/ml	90	94.4	78	94.9	0.4	-8.5	10.1*	6.165**	7.822	1.27	0.95	1.69
	≥0.15 mcg/ml	90	98.9	78	100	1.1	-8.2	5.2*					

Group 1: DTPa-HepB-IPV + Hib at 2, 4, and 6 months of age
Group 4: DTPa + HepB + Hib + OPV at 2, 4, and 6 months of age
N = number of subjects tested
‡ Definition of seroprotection/vaccine response provided in Section 3.2.2.
§Clinical limit = GMT ratio of 1.5 for all anti-pertussis antibodies (anti-PT, anti-FHA, and anti-PRN); 2.0 for anti-HBs
*Upper limit of 90% CI below clinical limit for non-inferiority
**supportive parameter of secondary interest (clinical limit for non-inferiority was not specified for these antigens)

Reviewer comment: Differences in seroprotection/vaccine response rates between Group 1 and Group 4 as well as GMT ratios between Group 1 and Group 4 one month after completion of the three-dose primary vaccination course in subjects included in the according to protocol (ATP) immunogenicity analyses were within the pre-specified clinical limits for non-inferiority with the exception of vaccine response rates for FHA **(bolded)**.

3.2.4 Pivotal Study: DTPa-HepB-IPV-044 (Lot Consistency and Manufacturing Bridge)

Title: A double-blind randomized primary vaccination study to evaluate the lot-to-lot consistency of DTPa-HepB-IPV vaccine manufactured according to the new manufacturing process and to bridge the DTPa-HepB-IPV vaccine manufactured according to the new manufacturing process with the DTPa-HepB-IPV vaccine manufactured by the initial manufacturing process administered to infants at 2, 4, and 6 months of age co-administered with Hib vaccine (OmniHIB™) in a separate injection.

Location: USA

Study Period: 2/11/98-2/3/99

Investigators:

Mark M. Blatter, MD: Pittsburgh Pediatric Research
Douglas Eisert, MD: Wenatchee Valley Clinic, WA
Gerald W. Bottenfield, MD: R/D Clinical Research, Inc., Lake Jackson, TX
James M. McCarty, MD: Hill Top Research, Inc., Fresno, CA
Kathryn M. Edwards, MD: Vanderbilt University School of Medicine, TN

Beth W. Nauert, MD: Center for Clinical Research, Austin, TX

Objectives:

Primary Objective:
- To evaluate the lot-to-lot consistency in terms of immunogenicity for three production lots of DTPa-HepB-IPV vaccine manufactured according to the new manufacturing process (second lot series)

Secondary Objectives:
- To evaluate the lot-to-lot consistency in terms of reactogenicity for three production lots of DTPa-HepB-IPV vaccine manufactured according to the new manufacturing process (second lot series)
- To evaluate whether DTPa-HepB-IPV vaccine manufactured according to the new manufacturing process (second lot series) results in decreased immunogenicity as compared to DTPa-HepB-IPV vaccine manufactured according to the initial manufacturing process (first lot series): Manufacturing bridge from first to second lot series for immunogenicity
- To evaluate whether DTPa-HepB-IPV vaccine manufactured according to the new manufacturing process (second lot series) results in increased reactogenicity as compared to DTPa-HepB-IPV vaccine manufactured according to the initial manufacturing process (first lot series): Manufacturing bridge from first to second lot series for safety

Schedule: 2, 4, 6 months of age
(6-12 weeks at time of first vaccination)

Group 1: DTPa-HepB-IPV, Lot A 2nd lot series + Hib (OmniHIB™)
Group 2: DTPa-HepB-IPV, Lot B 2nd lot series + Hib (OmniHIB™)
Group 3: DTPa-HepB-IPV, Lot C 2nd lot series + Hib (OmniHIB™)
Group 4: DTPa-HepB-IPV, 1st lot series + Hib (OmniHIB™)

Number of subjects

Number of subjects: Enrolled (ITT Cohort): 484 at five centers (Note: six centers were initiated but one of the six centers did not enroll any subjects)

According-to-Protocol (ATP) safety analysis: 477
ATP Immunogenicity analysis (primary analysis): 434
Population group: Healthy infants, 6 to 12 weeks of age at the time of the first vaccination

Data analysis for immunogenicity

For each treatment group, and for the pooled second series lots, the seropositivity rates/seroprotection rates/vaccine response rates one month after the third vaccination and their exact 95% CIs were calculated. Antibody titers were summarized by GMTs with their 95% CIs and Reverse Cumulative Distribution Curves.

Primary objective: For evaluation of the lot-to-lot consistency, the pairwise differences between Group 1 and Group 2, Group 1 and Group 3, and Group 2 and Group 3 were evaluated using 90% CIs for primary and secondary parameters. The primary objective, i.e., consistency of the three second series production lots of DTPa-HepB-IPV vaccine, was reached if for all primary parameters each set of 90% confidence intervals for pairwise differences were within the clinical limits defining equivalence for differences in vaccine response/ seroprotection rates [-10%; +10%] and for GMT ratios for anti-PT, anti-PRN and anti-FHA [0.67; 1.5].

Secondary objective: The non-inferiority of the second series formulation (pooled Groups 1, 2 and 3) as compared to the first series formulation (Group 4) was also evaluated using 90% CIs for primary parameters and secondary parameters. If the primary objective was reached, the second series formulation was considered at

least as immunogenic as the first series formulation, if the upper limits of the exact 90% CI of treatment effect were below the clinical limits defining non-inferiority for all primary parameters.

Primary objective: Lot-to-lot consistency

DTPa-HepB-IPV-044: Seroprotection/vaccine response rates for Group 1, Group 2 and Group 3 with maximum 90% CI limits of pairwise differences for subjects (ATP cohort for immunogenicity)

Endpoints	Group 1		Group 2		Group 3		Maximum 90% CI limit of pairwise differences*
	N	Rate (%)	N	Rate (%)	N	Rate (%)	
anti-D > 0.1 IU/mL‡	107	100	112	100	109	99.1	7.0%**
anti-T > 0.1 IU/mL‡	107	100	112	100	109	100	5.5%**
Vaccine response to PT‡	107	100	112	99.1	109	100	6.8%**
Vaccine response to FHA‡	**97**	**99.0**	**104**	**96.2**	**102**	**100**	**11.4%**
Vaccine response to PRN‡	**107**	**91.6**	**112**	**83.9**	**109**	**91.7**	**17.8%**
anti-HBs > 10 mIU/mL‡	107	99.1	112	98.2	109	100	8.2%**
anti-Polio 1 > 8‡	107	100	111	100	108	100	5.6%**
anti-Polio 2 > 8‡	107	100	111	100	108	100	5.6%**
anti-Polio 3 > 8‡	107	100	110	100	108	100	5.6%**
anti-PRP > 1.0 mcg/mL†	107	92.5	112	89.3	109	90.8	12.5%
anti-PRP > 0.15 mcg/mL†	107	100	112	100	109	100	5.5%

Group 1: DTPa-HBV-IPV, second series Lot A + Hib
Group 2: DTPa-HBV-IPV, second series Lot B + Hib
Group 3: DTPa-HBV-IPV, second series Lot C + Hib
N = number of subjects tested
* highest value among the limits of exact 90% CIs for all pairwise differences between groups 1, 2, and 3
**Maximum 90% CI limit of pairwise differences below clinical limit for equivalence
Clinical limit = 10% difference in seroprotection rates except for anti-PRP > 0.15 mcg/mL where limit = 5% difference
Vaccine response to PT, FHA, and PRN was defined as appearance of antibodies in subjects who were initially seronegative, and at least maintenance of prevaccination antibody titers in those who were initially seropositive.
‡: parameter of primary interest
† supportive parameter of secondary interest

Reviewer comment: When the immune response in terms of seroresponse/vaccine response rates to lots A, B, and C in the second lot series underwent pairwise comparison, the difference in seroresponse/vaccine response rate was within the prespecified limit of 10% for equivalence (lot consistency), with the exception of the response rates to pertactin and FHA **(bolded)**.

DTPa-HepB-IPV-044: Post-vaccination GMTs in Group 1, Group 2 and Group 3 with maximum 90% CI limits of pairwise ratios (ATP cohort for immunogenicity)

Endpoints	Group 1		Group 2		Group 3		Maximum 90% CI limit of pairwise ratio*
	N	GMT	N	GMT	N	GMT	
anti-D†	107	1.050	112	1.049	109	1.047	1.22
anti-T†	107	2.651	112	2.561	109	2.910	1.34
anti-PT‡	107	93.1	112	99.1	109	105.3	1.30**
anti-FHA‡	97	164.4	104	151.0	102	190.2	1.41**
anti-PRN‡	**107**	**115.4**	**112**	**95.9**	**109**	**126.7**	**1.59**
anti-HBs§	107	1563.8	112	1575.5	109	1930.4	1.73**
anti-Polio 1†	107	295.3	111	320.6	108	371.5	1.60
anti-Polio 2†	107	277.7	111	288.3	108	406.4	1.86
anti-Polio 3†	107	848.3	110	800.9	108	1057.4	1.69
anti-PRP†	107	5.107	112	4.955	109	6.431	1.67

Group 1: DTPa-HBV-IPV, second series Lot A + Hib
Group 2: DTPa-HBV-IPV, second series Lot B+ Hib
Group 3: DTPa-HBV-IPV, second series Lot C + Hib
N = number of subjects tested
* highest value among the limits of 90% CIs for all pairwise ratios between groups 1, 2 and 3
** Maximum 90% CI limit of pairwise ratios below clinical limit for equivalence
Clinical limit = GMT ratio of 1.5 for all anti-pertussis antibodies (anti-PT, anti-FHA, and anti-PRN); 2.0 for anti-HBs
‡: parameter of primary interest
§: main parameter of secondary interest
† supportive parameter of secondary interest (clinical limit for non-inferiority was not specified for these endpoints)

Reviewer comment: With respect to the pairwise ratios of GMTs, the prespecified endpoints for non-inferiority between the three lots were met, with the exception of the GMTs to pertactin **(bolded)**.

To address the fact that the *a priori* clinical limits defining equivalence for lot-to-lot consistency were not met with respect to all pertussis antigens, the manufacturer hypothesized that high prevaccination titers affected the immune response to pertussis components. A reanalysis of the data was performed as follows:

Study DTPa-HepB-IPV-044: Re-analysis of the consistency of the Second Lot Series of the SBB DTPa-HepB-IPV vaccine in terms of the immune response to the pertussis antigens after adjustment for pre-vaccination titer: vaccine response calculated after elimination of subjects with high* pre-vaccination titers; GMT analyzed after adjustment for pre-vaccination titer (ANCOVA) (BLA Table 8.III.1.7)

Antigen	Vaccine Response†							GMT‡						
	Group 1		Group 2		Group 3		Max 90% CI limit for difference between lots	Group 1		Group 2		Group 3		Max 90% CI limit for ratio between lots
	N	%	N	%	N	%		N		N		N		
PT	106	100	109	100	111	99.1	6.9§	107	93	109	104	112	101	1.3§
FHA	**97**	**99.0**	**101**	**100**	**104**	**96.2**	**11.4**	97	165	102	187	104	152	1.4§
PRN	**97**	**96.9**	**104**	**95.2**	**101**	**92.1**	**14.9**	107	116	109	121	112	100	1.4§

Group 1: DTPa-HBV-IPV, second series Lot A+ Hib
Group 2: DTPa-HBV-IPV, second series Lot B + Hib
Group 3: DTPa-HBV-IPV, second series Lot C+ Hib
% = Percentage of subjects with VR
*Anti-PT titer ≥54 EL.U/ml; Anti-FHA titer ≥119 EL.U/ml; Anti-PRN titer ≥56 EL.U/ml

†VR definition: for pertussis antibodies: initially seronegative subjects with post-vaccination titer ≥ cut-off (5 EL.U/ml) or initially seropositive subjects with post-vaccination titer ≥ pre-vaccination titer
‡Units for Pertussis antibodies: EL.U/ml §Limit within clinical limits of equivalence

Reviewer comment: SBB hypothesized that failure to meet the equivalence criteria for demonstrating lot consistency with respect to pertactin and FHA may be due to an imbalance in the groups in the number of subjects with high prevaccination titers (from maternal antibodies) to pertussis antigens. However, even after excluding subjects with high pre-vaccination titers, the maximum difference between the lots still falls outside the prespecified limit of 10% with respect to vaccine response rates to FHA and pertactin **(bolded**). The adjusted GMTs, however, are within prespecified limits.

Supportive Data for Lot-to-lot Consistency of Second Lot Series

Additional data to support the lot-to-lot consistency of the second lot series were provided by studies DTPa-HepB-IPV/Hib-027 conducted in the US under a 2, 4, 6 month schedule. This study evaluated the same lots of DTPa-HepB-IPV used in DTPa-HepB-IPV-044 but evaluated SBB's DTPa-HepB-IPV/Hib vaccine (DTPa-HepB-IPV admixed with SBB's PRP-T prior to injection). DTPa-HepB-IPV/Hib is not licensed in the U.S. Lot-to-lot consistency testing for the three pertussis antigens PT, FHA, and pertactin was performed using an equivalence approach and the same prespecified criteria as in Study DTPa-HepB-IPV-044. Results are shown below.

Study DTPa-HepB-IPV/Hib-027: Differences in <u>vaccine response rates</u> to PT, FHA and PRN with their 90% CIs between paired consistency lots (Group 2 and Group 3, Group 2 and Group 4, and Group 3 and Group 4) -- ATP cohort for Immunogenicity (BLA amendment 8/3/00, Table 23.b-1)

Endpoints	Group 3		Group 2		Difference (Group 2 minus Group 3)		
	N	Rate (%)	N	Rate (%)	Difference of rates (%)	90% CI LL	90% CI UL
Vaccine response to PT	227	97.80	252	99.21	1.41	-1.48	5.09*
Vaccine response to FHA	206	99.03	226	98.67	-0.36	-3.88	2.85*
Vaccine response to PRN	230	94.35	253	96.84	2.49	-1.53	7.13*
	Group 4		Group 2		Difference (Group 2 minus Group 4)		
Vaccine response to PT	249	98.39	252	99.21	0.81	-2.09	3.94*
Vaccine response to FHA	241	99.17	226	98.67	-0.50	-3.85	2.40*
Vaccine response to PRN	251	95.62	253	96.84	1.22	-2.73	5.32*
	Group 4		Group 3		Difference (Group 3 minus Group 4)		
Vaccine response to PT	249	98.39	227	97.80	-0.59	-4.40	2.59*
Vaccine response to FHA	241	99.17	206	99.03	-0.14	-3.56	2.70*
Vaccine response to PRN	251	95.62	230	94.35	-1.27	-6.06	2.98*

Group 2: DTPa-HepB-IPV lot A mixed with Hib lot A
Group 3: DTPa-HepB-IPV lot B mixed with Hib lot B
Group 4: DTPa-HepB-IPV lot C mixed with Hib lot C
N = number of subjects with pre- and post-vaccination results available
Vaccine response defined as appearance of antibodies in initially seronegative subjects and at least maintenance of pre-vaccination titers in initially seropositive subjects
*Upper and lower limits of 90% CIs within clinical limits for equivalence
Clinical limits = -10%, +10% difference in vaccine response rates

Study DTPa-HepB-IPV/Hib-027: Ratios of post-vaccination GMTs for anti-PT, anti-FHA, and anti-PRN with their 90% CIs between paired consistency lots (Group 2 and Group 3, Group 2 and Group 4, and Group 3 and Group 4) -- ATP cohort for immunogenicity (BLA amendment 8/3/00-Table 23.b-2)

Antibody	Group 2		Group 3		Group 2 divided by Group 3		
						90% CI	
	N	GMT	N	GMT	Ratio of GMTs	LL	UL
anti-PT	302	70.7	274	82.3	0.86	0.79	0.94*
anti-FHA	273	321.7	248	296.2	1.09	1.00	1.18*
anti-PRN	303	116.1	276	122.8	0.95	0.84	1.07*
	Group 2		Group 4		Group 2 divided by Group 4		
anti-PT	302	70.7	289	70.7	1.00	0.92	1.09*
anti-FHA	273	321.7	281	322.5	1.00	0.92	1.08*
anti-PRN	303	116.1	290	114.6	1.01	0.90	1.14*
	Group 3		Group 4		Group 3 divided by Group 4		
anti-PT	274	82.3	289	70.7	1.16	1.07	1.27*
anti-FHA	248	296.2	281	322.5	0.92	0.84	1.00*
anti-PRN	276	122.8	290	114.6	1.07	0.95	1.21*

Group 2: DTPa-HepB-IPV lot A mixed with Hib lot A
Group 3: DTPa-HepB-IPV lot B mixed with Hib lot B
Group 4: DTPa-HepB-IPV lot C mixed with Hib lot C
N = number of subjects with available results
*Upper and lower limits of 90% CIs within clinical limits for equivalence
Clinical limits = GMT ratio between 0.67, 1.5

Reviewer comment: Data from Study DTPa-HepB-IPV/Hib-027 utilized the same lots of DTPa-HepB-IPV as in DTPa-HepB-IPV. In these studies, all prespecified pertussis immunogenicity endpoints for demonstrating lot-to-lot consistency of the second lot series were met.

In addition, DTPa-HepB-IPV/Hib-027 included a comparison with separately administered U.S. licensed vaccines DTPa, hepatitis B, OPV and Hib (Infanrix®, Engerix-B®, ORIUME®, and OmniHIB™, respectively), allowing a direct comparison of the pertussis immune responses of DTPa-HepB-IPV/Hib and separately administered Infanrix®.

DTPa-HepB-IPV/Hib-027 – Vaccine response rates and GMTs to pertussis antigens-ATP cohort

Vaccine Response					GMT		
Antibody	**Group 1**						
	N	**%**	**95% CI**			**95% CI**	
			LL	**UL**		**LL**	**UL**
Anti-PT	260	100.0	98.6	100	54.2	50.3	58.3
Anti-FHA	245	100	98.5	100	332.9	309.5	358.1
Anti-PRN	260	100	98.6	38.0	112.0	100.5	124.7
	Group 2						
Anti-PT	302	100	98.8	100	70.7	65.9	75.9
Anti-FHA	273	100	98.7	100	321.7	299.6	345.5
Anti-PRN	303	99.3	97.3	99.9	116.1	104.8	128.8
	Group 3						
Anti-PT	274	100	98.7	100	82.3	76.7	88.4
Anti-FHA	248	100	98.5	100	296.2	275.4	318.6
Anti-PRN	276	100	98.7	100	122.8	110.8	136.0
	Group 4						
Anti-PT	289	100.0	98.7	100	70.7	65.5	76.3
Anti-FHA	281	100	98.7	100	322.5	301.6	344.8
Anti-PRN	290	100	98.7	100	114.6	104.3	125.9
	Pooled groups 2, 3, 4						
Anti-PT	865	100	99.6	100	74.2	71.1	77.4
Anti-FHA	802	100	99.5	100	313.9	301.4	326.8
Anti-PRN	869	99.8	99.2	100	117.7	111.1	124.7

Group 1: DTPa + HepB + OPV + Hib
Group 2: DTPa-HepB-IPV lot A mixed with Hib lot A
Group 3: DTPa-HepB-IPV lot B mixed with Hib lot B
Group 4: DTPa-HepB-IPV lot C mixed with Hib lot C
N = number of subjects with results available
%=percentage of seropositive subjects
Vaccine response defined as appearance of antibodies in initially seronegative subjects and at least maintenance of pre-vaccination titers in initially seropositive subjects

Reviewer comment: Unlike Study DTPa-HepB-IPV-044, Study DTPa-HepB-IPV/Hib-027 included a control group receiving separately administered Infanrix®. Immune responses to pertussis components (vaccine response and GMTs) were comparable between individual lots of DTPa-HepB-IPV/Hib as well pooled lots of DTPa-HepB-IPV/Hib and separately administered DTPa, HepB, OPV and Hib.

Manufacturing bridge: 1st to 2nd lot series

DTPa-HepB-IPV-044: Comparison of the immunogenicity of the First and Second Lot Series vaccine (BLA Table 8.III.1-10)

Antigen	Seroprotection/Vaccine response*							GMT†						
	2nd Lot Series‡		1st lot Series§		1st minus 2nd Lot Series			2nd Lot Series‡		1st lot Series§		1st divided by 2nd Lot Series		
	N	%	N	%	%	90% CI		N	%	N	%		90% CI	
						LL	UL						LL	UL
Diphtheria	328	99.7	106	99.1	-0.6	-5.4	1.9 ¶	—	—	—	—	—	—	—
Tetanus	328	100	106	100	0	-4.2	1.9 ¶	—	—	—	—	—	—	—
PT	328	99.7	104	99.0	-0.7	-5.6	1.8 ¶	328	99	106	101	1.0	0.9	1.1¶
FHA	303	98.3	99	96.0	-2.4	-8.7	1.8 ¶	303	168	101	163	1.0	0.9	1.1¶
PRN	**328**	**89.0**	**104**	**95.2**	**6.2**	**-0.5**	**12.3**	328	112	106	133	1.2	1.0	1.4¶
HBs	328	99.1	106	99.1	0	-5.1	2.8 ¶	328	1682	106	1455	0.9	0.7	1.1¶
Polio 1	326	100	105	100	0	-4.3	1.9 ¶	—	—	—	—	—	—	—
Polio 2	326	100	105	100	0	-4.3	1.9 ¶	—	—	—	—	—	—	—
Polio 3	325	100	105	100	0	-4.3	1.9 ¶	—	—	—	—	—	—	—

% = Percentage of subjects with SP/ VR
— = No pre-specified limit of non-inferiority
†Units: •Pertussis antibodies: EL.U/ml
•HBs antibodies: mIU/ml
•Polio: None
‡Pooled data from lots Second Lot Series (Lots A, B, C) §First Lot Series ¶Upper limit below clinical limit for non-inferiority

Reviewer comment: With respect to manufacturing bridging from the 1st lot series to 2nd lot series, SBB met their prespecified endpoints with the exception of vaccine response rates to pertactin **(bolded)**.

To address the fact that the *a priori* clinical limits defining equivalence for manufacturing bridging were not met with respect to all pertussis antigens, the manufacturer hypothesized that high prevaccination titers (from maternal antibodies) affected the immune response to pertussis components. A reanalysis of the data was performed as follows:

Study DTPa-HepB-IPV-044: 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 the immune response to the pertussis antigens after adjustment for pre-vaccination titer: vaccine response calculated after elimination of subjects with high* pre-vaccination titers; GMT analyzed after adjustment for pre-vaccination titer (ANCOVA) (Table 8.III.1- 11)

Antigen	VR†							GMT (EL.U/ml)						
	2nd Lot Series‡		1st lot Series		1st minus 2nd Lot Series			2nd Lot Series‡		1st lot Series		1st divided by 2nd Lot Series		
	N	%	N	%	%	90% CI		N		N			90% CI	
						LL	UL						LL	UL
PT	326	99.7	103	100	0.3	-3.9	2.9¶	328	99	104	102	1.0	1.0	1.2¶
FHA	302	98.3	94	100	1.7	-3.1	5.2¶	303	167	99	165	1.0	0.9	1.1¶
PRN	302	94.7	98	99.0	5.3	0.4	9.8¶	328	112	104	132	1.2	1.0	1.3¶

% = Percentage of subjects with VR
*Anti-PT titer ³54 EL.U/ml; Anti-FHA titer ³119 EL.U/ml; Anti-PRN titer ³56 EL.U/ml
†VR definition:
•Pertussis antibodies:
– initially seronegative subjects with post-vaccination titer ³ cut-off (5 EL.U/ml)
– initially seropositive subjects with post-vaccination titer ³ pre-vaccination titer
‡Pooled data from A, B, C
¶Upper limit below clinical limit for non-inferiority

Reviewer comment: As was done in the evaluation of lot consistency, SBB performed a reanalysis of vaccine response rates adjusting for high prevaccination antibody titers. Under this reanalysis, the prespecified criteria for non-inferiority with respect to the pertussis antigens were met for the comparison between the first and second lot series.

Summary of data supporting lot-to-lot consistency and manufacturing bridge: In Study DTPa-HepB-IPV-044, SBB met all prespecified endpoints for demonstrating lot-to-lot consistency of the 2nd lot series, with the exception of the immune response to FHA (vaccine response rate) pertactin (vaccine response rate and GMT). SBB also did not meet their prespecified immunogenicity endpoints with respect to pertactin for the manufacturing bridge between the 1st and 2nd lot series. When a re-analysis was performed eliminating those subjects with high prevaccination titers to pertussis components, prespecified criteria for manufacturing bridging from the first to second lot series were met. However, for lot consistency, comparison between the three lots with respect to the vaccine response to pertactin and FHA exceeded the prespecified limit.

Of note, Reverse Cumulative Distribution (RCD) curves (not shown) of the immune responses to pertussis antigens shows that virtually all infants (regardless of lot administered) demonstrated an immune response to each pertussis component. Pairwise comparison of the three lots demonstrates that one lot of the second lot series appeared to elicit lower immune response to FHA and pertactin than the other two lots; this lot may account at least in part for the failure to meet prespecified criteria for lot consistency and manufacturing bridging.

To provide further support for consistency of the second lot series, SBB submitted data from DTPa-HepB-IPV/Hib-027 (lot consistency study of SBB's DTPa-HepB-IPV admixed with Hib prior to injection) utilized identical lots of DTPa-HepB-IPV as those used in Study DTPa-HepB-IPV-044. DTPa-HepB-IPV/Hib-027 met all pre-specified endpoints for pertussis antigens for demonstrating lot-to-lot consistency. In addition, DTPa-HepB-IPV/Hib included a comparison arm with separately administered vaccines including DTPa (Infanrix®). The immune response to pertussis components elicited by the three lots of DTPa-HepB-IPV admixed with Hib demonstrated comparable immune response to those of Infanrix®.

The clinical relevance of the observed difference in the immune response to FHA and pertactin is unclear because there exists no generally accepted immunologic correlate(s) of protection against pertussis. One U.S. licensed acellular pertussis vaccine (Certiva) contains only pertussis toxoid. For all studies in the BLA, the database was searched for the occurrence of pertussis disease. Only one subject was diagnosed with pertussis (subject # 4255 from DTPa-HepB-IPV-011) based on clinical symptomatology. This infant received DTPa-HepB-IPV at approximately 2, 3 and 4 months of age. Fifteen days after the third dose she was hospitalized for 3 days for apnea, cyanosis and a pertussis-like cough. No confirmatory testing was performed. One DTPa-HepB-IPV recipient experienced a "pertussoid fit of coughing" 3 days after the first dose. No confirmatory testing was performed. The patient recovered and went on to receive two subsequent doses uneventfully.

3.2.5 Hepatitis B Vaccine Schedule Change

The recommended schedule for administration of Engerix-B®, SBB's U.S. licensed hepatitis B vaccine, in infants is a 0, 1 and 6 month schedule. Under this BLA, SBB seeks an indication for DTPa-HepB-IPV administration on a 2, 4, and 6 month schedule. Summary data on the immune response to HBs for all studies submitted as part of the BLA are presented below.

A. Summary BLA Studies: Hepatitis B immunogenicity in infants receiving DTPa-HepB-IPV - Effect of Variations in Schedule on Seroprotection and GMT

Study	Lab	N	Seroprotection %	[95%CI]	GMT	[95%CI]
2, 4, 6 months						
002	SBB	19	100	[79.1-100]	1517	[875-2630]
004	SBB	46	100	[90.4-100]	1398	[952-2054]
015	MEP	89	100	[95.9-100]	1661	[1256-2198]
044 (pooled 2nd lot)	MEP	328	99.1	[97.4-99.8]	1682	[1428-1980]
044 (1st lot)	MEP	106	99.1	[94.9-100]	1455	[1108-1911]
3, 4, 5 months						
001	SBB	17	100	[77.1-100]	707	[448-1115]
005	SBB	343	97.7	[95.3-98.9]	376	[320-441]
016	MEP	161	98.8	[98.8-99.8]	484	[386-608]
3, 4.5, 6 months						
012	SBB	507	99.6	[98.6-100]	890	[798-992]
019	MEP	45	100	[90.2-100]	2070	[1515-2829]
2, 3, 4 months						
017	MEP	23	95.7	[76.0-99.8]	472	[231-964]
1.5, 2.5, 3.5 months						
030	MEP	150	98.7	[95.3-99.8]	1016	[835-1237]

Reviewer comment: Clinical studies of hepatitis B vaccines have defined a protective antibody (anti-HBs) level as $\geq$ 10 mIU/mL. The observed anti-HBs response in infants receiving DTPa-HepB-IPV was significantly greater than the level considered protective against hepatitis B disease. In the three BLA studies administering DTPa-HepB-IPV on the proposed 2, 4, 6 month schedule, 99.1- 100% considered seroprotective, with GMTs from 1455 to 1661 mIU/mL.

Because administration of DTPa-HepB-IPV on a 2, 4, 6 month schedule differs from the licensed schedule of its hepatitis B vaccine component, Engerix-B®, data were sought demonstrating that the HBs immune responses for both schedules were comparable. Study DTPa-HepB-IPV-015 (see section 3.2.3) compared DTPa-HepB-IPV + Hib (group 1) with separately administered DTPa, HepB, OPV and

Hib (group 4), but both groups received vaccinations on a 2, 4, and 6 schedule. Both groups achieved 100% seroprotection, but the GMTs for the group receiving DTPa-HepB-IPV (group 1) were 1661 mIU/mL compared with 805 mIU/mL for the group receiving separately administered Engerix-B® (group 4). No data were submitted as part of the BLA directly comparing the anti-HBs immune response of DTPa-HepB-IPV to the immune response Engerix-B® administered at birth, 1 and 6 months. Supportive data for the change in schedule for the hepatitis B component, were submitted from Study DTPa-HepB-030 which evaluated SBB's DTPa-HepB combination (not licensed in the U.S.)

B. DTPa-HepB-030: Supportive Study for Schedule Change for Hepatitis B Component

Title: An Open Study of the Safety and Immunogenicity of DTPa-HepB Vaccine Administered as a Single Injection at 2, 4, and 6 Months of Age as Compared to Engerix-B® [Hepatitis B Vaccine (Recombinant)] Administered at Birth, 1, and 6 Months of Age and DTPa Vaccine Administered at 2, 4, and 6 Months of Age.

Location: USA

Investigators: Joel Ward, MD

Study Date (Started/Completed): April 1996-March 1997

Objective:

Primary Objective: (Immunogenicity)

To evaluate the immune response to the hepatitis B component of the combined DTPa-HB vaccine administered as a single injection at 2, 4, and 6 months of age as compared to the response to Engerix-B® administered at birth, 1, and 6 months of age.

Methodology:

Open, randomized, controlled trial

Number of subjects

Enrolled (ITT cohort): 280 (140 each group)
Completed: 210
ATP cohort for safety: 265
ATP cohort for immunogenicity: 204

Population: Healthy infants, between birth and 7 days of age at time of enrollment.

Schedule:

Group 1 - DTPa-HepB + Hib + OPV (at 2, 4, and 6 months of age):
Group 2 - DTPa + Hib + OPV (at 2, 4, and 6 months of age) and HepB (at birth, 1 and 6 months of age)

DTPa-HepB-030: Immunogenicity of a three dose primary vaccination of the HepB antigen administered either as combined DTPa-HepB vaccine at 2, 4, and 6 months or as a separately-administered U.S.-licensed HepB vaccine at 0, 1, 6 months of age (Table 8.III.1-18)

Antigen	Vaccine (Schedule)	N	Seroprotection*		GMT (mIU/ml)	
			%	95%CI		95%CI
HBs	DTPa-HepB (2, 4, 6 mo)	99	99.0	94.5-100	1052	804-1377
	HepB (0, 1, 6 mo)	105	100	96.5-100	3717	2929-4718

*Seroprotection definition: subjects with post-vaccination titer $\geq$ 10 mIU/ml

Reviewer comment: Seroprotection for hepatitis B, defined as subjects with post-vaccination titers of $\geq$ 10 mIU/mL, was the primary immunogenicity endpoint, anti-HBs GMTs were considered a secondary endpoint.

DTPa-HepB-030: Comparison of the immunogenicity of a three-primary vaccination of the HepB antigen administered as a combined DTPa-HepB vaccine at 2, 4, 6 months of age and as a U.S.-licensed HepB vaccine at 0, 1, 6 months of age (Table 8.III.1-19)

Seroprotection*					GMT (mIU/ml)				
Hep B (2, 4, 6 mo)	DTPa-HepB (0, 1, 6 mo)	HepB (0, 1, 6 mo) minus DTPa-HepB (2, 4, 6 mo)			HepB (0,1,6mo)	DTPa-HepB (2,4,6mo)	HepB (0, 1, 6 mo) divided by DTPa-HepB (2, 4, 6mo)		
%	%	%	90%CI					90%CI	
			LL	UL				LL	UL
99.0	100	1.0	-4.1	7.1**	**3717**	**1052**	**3.5**	**2.6**	**4.8**

% = Percentage of subjects with a response
*Seroprotection definition: Subjects with post-vaccination titers $\geq$ 10 mIU/ml; Clinical limit = 10% difference in seroprotection rate
**Upper limit below statistical limit for non-inferiority` Clinical limit = GMT ratio of 2.0

Reviewer comment: The immunogenicity of DTPa-HepB combination on a 2, 4, 6 month schedule compared with the standard 0, 1 and 6 month schedule met the prespecified criteria for non-inferiority with respect to seroprotection (upper limit on the confidence interval of 7.1%), with 99.0% of subjects given the 2, 4, 6 month schedule having post vaccination $\geq$ 10 mIU/mL, a level correlated with protection. The anti-HBs GMT was lower when the hepatitis B antigen was given on a 2, 4, 6 month schedule as part of the DTPa-HepB combination, compared with hepatitis B vaccine given on a 0, 1 and 6 months schedule. However, the anti-HBs immune response of the DTPa-HepB combination was well above the level considered to be protective.

C. Immune response to DTPa-HepB-IPV at 2, 4, 6 months of age following a birth dose of Hepatitis B vaccine

Two submitted studies provided data on the immune response to the hepatitis B component following a birth dose of hepatitis B vaccine The first study involved DTPa-HepB-IPV and the second study evaluated SBB's DTPa-HepB-IPV/Hib vaccine (not licensed in the U.S.)

1) Supportive study **DTPa-HepB-IPV-030,** conducted in Moldova, evaluated the use of DTPa-HepB-IPV on a 6, 10, and 14 week schedule following a birth dose of hepatitis B vaccine (Engerix-®). The comparator group received a birth dose of Engerix-B® followed by a combination vaccine containing whole cell pertussis, DTwP-IPV-Hib (not U.S. licensed) and Engerix- B® at 6, 10 and 14 weeks of age (group 2). Sera were obtained approximately 1 month following the third dose. Seroprotection rates for both groups were 98.7% for group 1 and 98.0% for the group 2, with GMTs for Group 1 1016.2 mIU/mL (90% CI = 834.6-1237.2) and GMTs for Group 2

426.6 mIU/mL (90% CI = 336.4 –540.7). This study, however, did not provide data on the proposed U.S. schedule (2, 4 and 6 months) for DTPa-HepB-IPV.

2) SBB has submitted supportive immunogenicity data from **DTPa-HepB-IPV/Hib-003** evaluating the safety and immunogenicity of a primary series of DTPa-HepB-IPV admixed with Hib, with and without a birth dose of hepatitis B vaccine. (See Section 3.3 for study synopsis) In this study, DTPa-HepB-IPV/Hib was administered at 2, 4 and 6 months. The immune response data from this study are presented below.

DTPa-HepB-IPV/Hib-003: Difference in anti-HBs immunological response with and without birth dose of hepatitis B vaccine – ATP cohort for immunogenicity

Group	N	Seroprotection Rate %	GMT
Group 1	84	100%	1240.1
Group 2	86	100%	2996.2
Difference between groups (90% CI)		**Group 1-Group 2**	**GMT ratio Group 1/Group 2**
		0% (-5.4%, 6.9%)*	0.414 (0.309, 0.554)*

Group 1: DTPa-HepB-IPV/Hib at 2, 4, 6 months without birth dose of hepatitis B vaccine (3 doses of HepB)
Group 2: DTPa-HepB-IPV/Hib at 2, 4, and 6 months following a birth dose of hepatitis B (4 doses of HepB)
* = upper limit of the 90% CI below the non-inferiority limit; 10% for the difference in seroprotection rate; 2 for the GMT ratio

Reviewer comment: Both groups of infants receiving DTPa-HepB-IPV/Hib at 2, 4, and 6 months of age, with or without a birth dose of hepatitis B vaccine, demonstrated 100% seroprotection to the hepatitis B component. The immune response in terms of GMTs was noticeably higher in the group receiving DTPa-HepB-IPV/Hib following a birth dose of hepatitis B vaccine (four doses of HepB).

3.3 Safety Data

3.3.1 Safety Database: DTPa-HepB-IPV for Primary Series Immunization (Doses 1-3)

DTPa-HepB-IPV Study	Schedule (mo)	# Receiving at Least One Dose* (Total Cohort)†	# eceiving at Least One Dose (ITT)‡	# Receiving at Least One Dose (ATP)§	Total # Doses (Total Cohort)	Total # Doses (ITT)	Total # Doses (ATP)
001 (S)*	3, 4, 5	20	20	20	54	54	54
002 (S)	2, 4, 6	30	30	30	87	87	87
004 (S)	2, 4, 6	50	50	50	149	149	149
005 (S)	3, 4, 5	567	565	561	1,694	1,681	1,669
011 (P)**	**3, 4, 5**	**4,695**	**4,666**	**3,027**	**13,926**	**13,859**	**9,032**
012 (S)	3, 4.5, 6	549	549	549	1,636	1,635	1,635
015 (P)	**2, 4, 6**	**200**	**200**	**200**	**483**	**483**	**483**
016 (S)	3, 4, 5	184	182	180	546	544	538
017 (S)	2, 3, 4	29	29	29	87	87	87
019 (S)	3, 4.5, 6	60	60	60	177	177	177
030 (S)	1.5., 2.5, 3.5	160	160	160	478	475	475
044 (P)	**2, 4, 6**	**484**	**482**	**476**	**1422**	**1,418**	**1,402**
Total (P)		**5, 379**	**5,348**	**3,703**	**15,831**	**15,760**	**10,917**
Total (P+S)		**7,028**	**6,993**	**5,342**	**20,739**	**20,649**	**15,788**
Total on 2, 4, 6 months schedule		**764**	**762**	**756**	**2141**	**2137**	**2121**

*Supportive **Pivotal

†Total Cohort: All subjects receiving at least one dose, regardless of whether a symptom sheet was completed
‡Intent-to-Treat (ITT) Cohort: Subjects who received the indicated vaccine and for whom at least one symptom sheet was completed.
§According-to-Protocol (ATP) cohort: Subjects who received the indicated vaccine dose and for whom at least one symptom sheet was completed and who were eligible for the ATP analysis.

3.3.2 Assessment of Safety

A. Statistical Analyses

Study cohorts for safety:

Intent-to-treat (ITT) cohort of safety: subjects who had received at least one dose of study vaccine and who had safety follow-up (at least one symptom sheet returned) after vaccination.

According-to-Protocol (ATP) cohort of safety. The ATP population was comprised of subjects who had received at least one dose of study vaccine according to their random assignment, who had safety follow-up after vaccination, who had not received a vaccine not specified or forbidden in the protocol and, in the case of double-blinded studies, for whom the randomization code was not broken.

For six of the twelve studies, the ATP safety cohort did not exclude any subjects (i.e., the ATP cohort equaled the ITT cohort). For five of the six remaining studies (DTPa-HepB-IPV-005**,-015**,-016,-017and**-044**), the ATP safety cohort excluded less than 1.5% of the enrolled subjects. For study DTPa-HepB-IPV**-011**, the ATP cohort excluded subjects who were enrolled prior to an amendment allowing for the introduction of a control group consisting of separately administered U.S. licensed vaccines (approximately 35% of the enrolled subjects). 2.9% of subjects enrolled after the amendment were excluded. Reanalysis of the ITT safety cohort was performed only for studies which excluded > 1.5% of the enrolled subjects.

Endpoints:

1. For solicited symptoms, the following parameters were investigated:

   - Proportions of subjects reporting any Grade 3 solicited symptom during the solicited follow-up period after any vaccination (study DTPa-HepB-IPV-011)
   - Number and proportion of subjects reporting each specified local or general symptom (overall and Grade 3) during the solicited follow-up period after any vaccination (studies DTPa-HepB-IPV-011,-015, -016, -030 and -044)
   - Number and proportion of doses with each specified local or general symptom during the solicited follow-up period after any dose and after each dose (all studies)
   - Number and proportion of doses with each specified local or general symptom rated as Grade 3 in intensity during the solicited follow-up period after any dose and after each dose (all studies except DTPa-HepB-IPV-001)

2. For unsolicited symptoms (reported from day 0 to day 30 after each vaccination), the following endpoints were investigated:

   - Number of doses followed by an AE classified by WHO Preferred Term (all studies contained in the BLA)
   - Number of doses followed by an AE classified by WHO Preferred Term with probable or suspected relationship to vaccination (all studies except DTPa-HepB-IPV-002 and –004)
   - Number and percentage of subjects experiencing unsolicited symptoms classified by WHO preferred term within 30 days after any vaccine dose (DTPa-HepB-IPV-011 and –044 only)

Analyses

With the exception of study DTPa-HepB-IPV-011, the evaluation of safety was limited to exploratory analyses.

1. For solicited symptoms, three statistical approaches were used (BLA Section 8.II.3):
   - Descriptive analyses: In studies DTPa-HepB-IPV-011, 015, -016, -030 and -044, exact 95% CIs were provided for the rate of solicited symptoms within each group. In addition for studies -011, -015, and -

044, the exact 90% CI for the difference between study groups in the percentage of subjects with a given symptom were provided.

- Hypothesis testing of no treatment difference: In studies DTPa-HepB-IPV-015, 016, -030 and -044, the study group differences in the proportions of subjects with solicited symptoms were evaluated by examining the overlapping of 95% CI between the groups
- Non-inferiority testing: This approach replaced the "hypothesis testing of no treatment difference". In Study DTPa-HepB-IPV-011, the 90% CI for the difference in the percentage of subjects with Grade 3 solicited symptoms over the vaccine course was obtained using the StatXact 3.0, exact CI for difference in proportions. Likewise, for each solicited symptom, 90% CIs for the difference in percentages of subjects with Grade 3 solicited symptoms were computed.

2. For unsolicited symptoms: Descriptive analyses were performed. In addition, DTPa-HepB-IPV-011 analyzed 90% CIs on the differences between the pooled DTPa-HepB-IPV groups and control group receiving U.S. licensed separately administered vaccines.

B. Solicited Symptoms (Local and General)

In each study, diary cards were maintained by the parents on the day of vaccination and each of three subsequent days (for a total of 4 days). Each of the pivotal studies involved parental assessment of local and systemic symptoms via diary cards for the day of vaccination (day 0) and each of three subsequent days (days 1-3 post-vaccination). In addition, Studies 015 and 044 included telephone follow up calls between days 1 and 3 post vaccination.

Definitions of Solicited Adverse Events

Local Symptoms (at injection site)	General (Systemic) Symptoms
Pain on digital pressure	Fever (rectal body temperature)*
Redness	Unusual crying for more than 1 hr
	Irritability/fussiness§
Swelling	Restlessness
	Loss of appetite
	Vomiting
	Diarrhea

*****All studies except for Study-001 (Supportive) had fever assessed via rectal temperature. Study-001 assessed axillary temperature with an adjusted scale.
§Irritability/fussiness with or without unusual crying was a solicited symptom in studies 015, 016, 017, 019, 030, 044.

Grading of Adverse Events:

Local Reactions:
If **redness or swelling** were present, the largest diameter was recorded.
Grade 1: <5 mm
Grade 2: 5-20 mm
Grade 3: >20 mm
Pain: Grade 0: absent
Grade 1: minor reaction with light touch
Grade 2: cried or protests to touch
Grade 3: cried when limb was moved

General Reactions:
Fever:

Grade 1: 38.0-38.5°C/100.4-101.3°F
Grade 2: 38.6-39.5°C/101.4-103.2°F
Grade 3: >39.5°C/>103.2°F

Grading of other general symptoms: (Note: some studies differed slightly with respect to solicited general symptoms. For example, 011 solicited the term "restlessness" and 015 solicited the term "fussiness".)

Grade 1: Adverse experience (AE) easily tolerated
Grade 2: AE sufficiently discomforting to interfere with daily activity
Grade 3: AE which prevented normal everyday activities

Irritability/Fussiness

Grade 0: child behaved as usual
Grade 1: child was slightly more irritable but had normal activity
Grade 2: prolonged crying and refused to play
Grade 3: persistent crying and refused to be comforted

C. Unsolicited Adverse Events

Definition of unsolicited adverse events: "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."

For the majority of studies, including DTPa-HepB-IPV-011and - 044, unsolicited adverse events were recorded for a period of up to 30 days following vaccination. For study 015, unsolicited AEs were recorded 14 days after each vaccination. Unsolicited data were pooled and classified according to World Health Organization (WHO) Body system and Preferred Term.

D. Serious Adverse Events (SAE)

A SAE was defined as any experience that, in the investigator's opinion, suggested a significant hazard to the vaccinee. SAEs were recorded during entire study period up to 30 days after 3rd vaccination. Parents/ guardians were instructed to immediately inform the investigator of the occurrence of any severe or serious sign or symptom at any time throughout the study period.

3.3.3 Pivotal Safety Study: DTPa-HBV-IPV-011

Title: Randomized clinical study to assess the safety and reactogenicity of SBB's DTPa-HepB-IPV vaccine when co-administered with Hib vaccine in two concomitant injections into opposite limbs, as a primary vaccination course to healthy infants at the age of 3, 4, and 5 months.

Location: Germany (90 sites)

Investigators: Principal: Dr. Fred Zepp, Mainz, Germany

Study Period (date of first to last visit): 11/16/95-12/18/97

Objective: The study ("pre-amendment period") was originally designed as a comparative safety study in which all subjects were randomized to receive SBB's DTPa-HepB-IPV concomitantly at separate sites along with one of four Hib vaccines (manufactured by SBB, Pasteur Merieux Connaught [PM, now known as Aventis Pasteur], Merck or Lederle) in a 1:1:1:1 fashion. After enrollment of 1569 subjects, the study was amended in order to allow for the introduction of a separate injection control group ("post-amendment period") consisting of Infanrix®, Act-HIB™, and ORIMUNE® (all US licensed).

Primary:
To assess the safety and reactogenicity of SBB's DTPa-HepB-IPV vaccine when co-administered with either SBB's Hib vaccine or with commercially available Hib vaccines, in comparison to co-administration of commercially available DTPa (Infanrix®), Hib (Act-HIB™, PMC) and OPV (ORIMUNE®) vaccines.

Secondary:
To investigate "less common" adverse events, i.e. adverse events that occur at a rate (per subjects) of 1% or less.

Statistical Methods:

Primary Endpoint: The difference between the pooled DTPa-HepB-IPV vaccine group and the control group in the percentage of subjects with grade 3 solicited symptoms over the full vaccination course was computed with its exact 90% CI (Stat Xact, difference between proportions). The primary objective was demonstrated if the lower limit of the 90% CI was above the –7.5% limit defining clinical non-inferiority.

Secondary Endpoint: To evaluate the secondary objective, the percentage of subjects experiencing unsolicited symptoms within 30 days after any vaccine dose, classified by WHO Preferred Terms, were tabulated by groups with their 95% CI. Asymptotic 90% CI of the differences in the percentages was provided to evaluate the non-inferiority of the pooled DTPa-HBV-IPV vaccine group as compared to the control group.

Population: Healthy infants, 8-16 weeks at the time of first vaccination

Design: Open, randomized **Schedule:** 3, 4, 5 months

Study Design:

Group 1 DTPa-HepB-IPV + SBB Hib
Group 2 DTPa-HepB-IPV + PMC Hib
Group 3 DTPa-HepB-IPV +Led Hib
Group 4 DTPa-HepB-IPV + Merck Hib*
Group 5 DTPa + PM Hib + OPV#

*Group 4 received 2 doses of Hib at 3 and 5 months of age
#Group 5 did not receive hepatitis B vaccine during the study period.

Total enrolled (ITT cohort):	5472
Total completed:	5318
Pooled Groups 1-4:	4696
Group 5:	776

Pre-amendment period: Enrolled: 1560; Completed 1513
Post-amendment period: Enrolled 3903; Completed 3805

ITT cohort for safety:	4666	
ATP cohort for safety:	Total:	3773
Pooled Groups 1-4:	3029	
Group 5:	744	

DTPa-HepB-IPV- 011: Site of Vaccine Administration			
Group	**Right anterolateral thigh**	**Left anterolateral thigh**	**Oral administration**
1	DTPa-HepB-IPV	Hib (SBB)	
2	DTPa-HepB-IPV	Act-HIB™	
3	DTPa-HepB-IPV	HibTITER™	
4	DTPa-HepB-IPV	PedvaxHib™*	
5**	DTPa (Infanrix®)	Act-HIB™	OPV (ORIMUNE®)

*Only administered at 3 and 5 months of age.
**Subjects in group 5 did not receive hepatitis B vaccine during the study period. Subjects in group 5 were offered Engerix B at the end of the study.

DTPa-HepB-IPV-011: Demographics

	Total	
Categories	**n**	**%**
Total	**5472***	
Black	**30**	**0.55**
White	**5260**	**96.13**
Asian	**122**	**2.23**
Not specified	**8**	**0.15**
Other	**52**	**0.95**
Female	**2655**	**48.52**
Male	**2816**	**51.46**

***ITT cohort (total enrolled)

Reviewer note: Wherever possible, data provided in this document for Study DTPa-HepB-IPV-011 has been provided for the ITT cohort for safety. In the BLA, many of the comparative tables (DTPa-HepB-IPV vs. separate administration control) of Study –011 were provided only for the ATP cohort for safety.

Primary Endpoint:

DTPa-HepB-IPV- 011: Percentage of subjects with Grade 3 solicited symptoms during the 4-day follow-up period over the full course of vaccination (any dose): ATP analysis

Symptom	**DTPa-HepB-IPV Pooled Groups 1-4* (N=3029)**				**Control Group 5 (N=744)**				**Group 5 minus Pooled Groups 1-4**		
			95% CI				**95% CI**		**Difference**	**90% CI**	
	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	1.41.	7.13
Local	236	7.8	6.9	8.8	90	12.1	9.8	14.7	4.3	2.15	6.83
General	318	10.5	9.4	11.6	94	12.6	10.3	15.2	2.1	-0.11	4.74

Group 1: DTPa-HepB-IPV + SBB Hib
Group 2: DTPa-HepB-IPV + PM 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 + PMC 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

Reviewer comment: During the vaccination course, 16.2% of subjects in the pooled DTPa-HepB-IPV vaccine group and 20.3% in the control group reported any solicited symptom graded 3 in intensity. The percentage of subjects with grade 3 solicited symptoms over the full vaccination course in the pooled groups receiving DTPa-HepB-IPV compared with the control group did not exceed the predefined –7.5% limit defining clinical non-inferiority.

Study DTaP-HepB-IPV-011 – Incidence of any and Grade 3 solicited local symptoms at the DTPa-based injection site, following dose 1, 2, 3 and any dose for pooled groups 1-4 and group 5 – ITT cohort (Adapted from SBB fax of 2/16/01)

Symptom		Groups 1-4 Pooled N=4668				Group 5 N=768				Groups 1-4 pooled minus Group %		
Dose 1		n	%	95%CI		N	%	95% CI		Diff.	90% CI	
				LL	UL			LL	UL	%	LL	UL
Pain	- any	653	14.0	13.0	15.0	109	14.21	11.80	16.9	-0.2	-2.7	2.1
	- grade 3	32	0.7	0.5	1.0	10	1.3	0.6	2.4	-0.6	-1.6	0.1
Redness	- any	866	18.6	17.5	19.7	124	16.1	13.6	18.9	2.4	--0.2	4.9
	- grade 3	57	1.2	0.9	1.6	14	1.8	1.0	3.0	-0.6	-1.7	0.2
Swelling	- any	591	12.7	11.7	13.7	74	9.6	7.6	11.9	3.0	0.8	5.1
	- grade 3	56	1.2	0.9	1.6	10	1.3	0.6	2.4	-0.1	-1.2	0.6
Dose 2												
Pain	- any	469	10.2	9.3	11.1	74	9.8	7.8	12.1	0.4	-1.8	2.4
	- grade 3	13	0.3	0.1	0.5	3	0.4	0.1	1.2	-0.1	-0.9	0.3
Redness	- any	1229	26.6	25.3	27.9	162	21.4	18.5	24.5	5.2	2.4	8.0
	- pain	46	1.0	0.7	1.3	5	0.7	0.2	1.5	0.3	-0.6	1.0
Swelling	- any	853	18.5	17.4	19.6	98	12.9	10.6	15.5	5.5	3.1	7.9
	- grade3	76	1.6	1.3	2.1	8	1.1	0.5	2.1	0.6	-0.4	1.4
Dose 3												
Pain	- any	452	9.9	9.0	10.8	61	8.1	6.3	10.3	1.7	-0.3	3.7
	- grade 3	12	0.3	0.1	0.5	1	0.1	0.0	0.7	0.1	-0.5	0.5
Redness	- any	**1171**	**25.6**	**24.3**	**26.9**	**156**	**20.8**	**17.9**	**23.9**	**4.8**	**2.0**	**7.6**
	- grade 3	49	1.1	0.8	1.4	8	1.1	0.5	2.1	0.0	-1.0	0.8
Swelling	- any	**842**	**18.4**	**17.3**	**19.6**	**102**	**13.6**	**11.2**	**16.3**	**4.8**	**2.3**	**7.2**
	- grade3	70	1.5	1.2	1.9	9	1.2	0.6	2.3	0.3	-0.7	1.2
Any dose												
Pain	- any	1075	23.0	21.8	24.3	171	22.3	19.4	25.4	0.8	-2.1	3.6
	- grade 3	55	1.2	0.9	1.5	12	1.6	0.8	2.7	-0.4	-1.5	0.4
Redness	- any	**1927**	**41.3**	**39.9**	**42.7**	**290**	**37.8**	**34.3**	**41.3**	**3.5**	**0.3**	**6.8**
	- grade 3	137	2.9	2.5	3.5	24	3.1	2.0	4.6	-0.2	-1.6	0.9
Swelling	- any	**1451**	**31.1**	**29.8**	**32.4**	**194**	**25.3**	**22.2**	**28.5**	**5.8**	**2.9**	**8.8**
	- grade 3	160	3.4	2.9	4.0	22	2.9	1.8	4.3	0.6	-0.8	1.8

Group 1- 4 pooled: DTPa-HBV-IPV vaccine concomitantly with Hib vaccine at a separate site
Group 5: SB's DTPa + PMC's PRP-T + Lederle's OPV
N = number of symptom sheets received. For groups 1-4 pooled N=4574-4668; for group 5 N = 750-768
n = number reporting the specific symptom
% = percentage reporting the specific symptom
CI = Confidence Interval; LL-UL = Lower and Upper Limit
In bold: symptoms for which the 90% CI failed to overlap 0% difference

Reviewer comment: The above table presents solicited local reactions at the DTPa-HepB-IPV injection site for pooled groups 1-4 and at the DTPa injection site for infants in group 5 who receiving separate DTPa, Hib and OPV. All infants in this study received only two injections at each vaccination visit

(DTPa-HepB-IPV + Hib in groups 1-4; DTPa + Hib in group 5). Local reactions were treated independently in SBB's analysis, with pain, redness and swelling assessed for each injection site separately. The analysis for the DTPa-based injection site is presented here because the DTPa-based injection site was generally more reactogenic for each dose than the Hib injection site for both pooled groups 1-4 and group 5. For dose 3 and any dose, redness and swelling were between 3.3 - 5.5% greater at the DTPa-HepB-IPV injection site (pooled groups 1-4) than at the DTPa injection site (group 5), with these differences statistically significant. The clinical relevance of this small increase in the incidence of redness and swelling is questionable, particularly because Grade 3 redness and swelling (largest diameter > 20 mm) were <u>not</u> different between study groups.

Because group 5 (separately administered vaccines) received only two concurrent injections at each vaccination visit (along with oral polio vaccine), the extent of local symptoms in the Study –011 control group may underestimate that of current clinical practice in the U.S. Under the U.S childhood immunization schedule, infants may receive as many as 5 separate injections.

Study DTaP-HepB-IPV-011 – Incidence of any and Grade 3 solicited general symptoms, following dose 1, 2, 3 and any dose for pooled groups 1-4 and group 5 – ITT cohort (Adapted from SBB fax of 2/16/01)

Symptom		Groups 1-4 Pooled N=4668				Group 5 N=768				Groups 1-4 Pooled minus Group 5		
		n	%	95%CI LL	UL	n	%	95% CI LL	UL	Difference %	90% CI LL	UL
Dose 1												
Fever	**T≥38°C**	**1173**	**25.1**	**23.9**	**26.4**	**100**	**13.0**	**10.7**	**15.6**	**12.0**	**9.5**	**14.4**
	T>39.5°C	14	0.3	0.2	0.5	2	0.3	0.0	0.9	0.0	-0.6	0.5
Loss of	- any	833	17.9	16.8	19.0	147	19.1	16.4	22.1	-1.3	-4.0	1.2
Appetite	- grade 3	28	0.6	0.4	0.9	4	0.5	0.1	1.3	0.1	-0.7	0.7
Restlessness	- any	1934	41.4	40.0	42.9	356	46.4	42.8	50.0	-4.9	-8.1	-1.7
	- grade 3	**142**	**3.0**	**2.6**	**3.6**	**44**	**5.7**	**4.2**	**7.6**	**-2.7**	**-4.4**	**-1.2**
Unusual	**-** any	1163	24.9	23.7	26.2	280	36.5	33.0	40.0	-11.5	-14.7	-8.5
crying	**- grade 3**	**182**	**3.9**	**3.4**	**4.5**	**52**	**6.8**	**5.1**	**8.8**	**-2.9**	**-4.7**	**-1.3**
Dose 2												
Fever	**T≥38°C**	**891**	**19.3**	**18.2**	**20.5**	**99**	**13.1**	**10.8**	**15.7**	**6.2**	**3.7**	**8.6**
	T>39.5°C	22	0.5	0.3	0.7	2	0.3	0.0	1.0	0.2	-0.5	0.7
Loss of	**- any**	**613**	**13.3**	**12.3**	**14.3**	**123**	**16.2**	**13.7**	**19.1**	**-3.0**	**-5.6**	**-0.6**
Appetite	**-** grade 3	24	0.5	0.3	8	5	0.7	0.2	1.5	-0.1	-1.0	0.4
Restlessness	**-** any	1480	32.0	30.7	33.4	265	35.0	31.6	38.5	-3.0	-6.2	0.1
	- grade 3	**71**	**1.5**	**1.2**	**1.9**	**23**	**3.0**	**1.9**	**4.5**	**-1.5**	**-2.9**	**-0.4**
Unusual	**- any**	**764**	**16.5**	**15.5**	**17.6**	**149**	**19.7**	**16.9**	**22.7**	**-3.1**	**-5.9**	**-0.6**
crying	- grade 3	77	1.7	1.3	2.1	16	2.1	1.2	3.4	-0.4	-1.7	0.5
Dose 3												
Fever	**T≥38°C**	**900**	**19.7**	**18.5**	**20.9**	**84**	**11.2**	**9.0**	**13.7**	**8.5**	**6.1**	**10.8**
	T>39.5°C	34	0.7	0.5	1.0	4	0.5	0.1	1.4	0.2	-0.6	0.8
Loss of	- any	572	12.5	11.6	13.5	85	11.3	9.2	13.8	1.2	-1.1	3.4
Appetite	- grade 3	20	0.4	0.3	0.7	0	0.0	0.0	0.5	0.4	-0.2	0.8
Restlessness	- any	1223	26.7	25.5	28.0	207	27.6	24.4	30.9	-0.9	-3.9	2.1
	- grade 3	71	1.6	1.2	2.0	13	1.7	0.9	2.9	-0.2	-1.4	0.7
Unusual crying	- any	601	13.1	12.2	14.2	107	14.3	11.8	17.0	-1.1	-3.6	1.1
	- grade 3	65	1.4	1.1	1.8	8	1.1	0.5	2.1	0.4	-0.7	1.2
Any dose												
Fever	**T≥38°C**	**2021**	**43.3**	**41.9**	**44.7**	**203**	**26.4**	**23.3**	**29.7**	**16.7**	**13.7**	**19.8**
	T>39.5°C	65	1.4	1.1	1.8	8	1.0	0.5	2.0	0.4	-0.6	1.2
Loss of	- any	1447	31.0	29.7	32.3	257	33.5	30.1	36.9	-2.5	-5.6	0.6
Appetite	- grade 3	64	1.4	1.1	1.7	8	1.0	0.5	2.0	0.3	-0.7	1.1
Restlessness	**- any**	**2728**	**58.4**	**57.0**	**59.9**	**475**	**61.8**	**58.3**	**65.3**	**-3.4**	**-6.6**	**-0.2**
	- grade 3	**249**	**5.3**	**4.7**	**6.0**	**66**	**8.6**	**6.7**	**10.8**	**-3.3**	**-5.3**	**-1.5**
Unusual	**- any**	**1771**	**37.9**	**36.5**	**39.3**	**374**	**48.7**	**45.1**	**52.3**	**-10.8**	**-14.0**	**-7.5**
crying	**-grade 3**	**289**	**6.2**	**5.5**	**6.9**	**71**	**9.2**	**7.3**	**11.5**	**-3.1**	**-5.1**	**-1.2**

Group 1-4 pooled: DTPa-HepB-IPV vaccine concomitantly with Hib vaccine at a separate site

Group 5: SBB's DTPa+PM Hib +OPV

N=number of symptom sheets received (for doses 1-3) or number of subjects with at least one symptom sheet received ("any dose"), with highest number reported

n=number reporting a specific symptom

%=percentage reporting the specific symptom

Onset of symptoms within 4 day follow up period (onset day 0-3)

In bold: symptoms for which the 90% CI failed to overlap the 0% difference

Reviewer comment: The incidence of fever $\geq$ 38°C in pooled groups receiving DTPa-HepB-IPV ranged from 25.1% following the first dose, to 19.7% following the 3rd dose. The incidence of fever following any dose (per subject) was 43.3%.

For each dose and over the full course of vaccination (any dose), the rate of fever (T $\geq$ 38°C) was increased in subjects receiving DTPa-HepB-IPV (pooled groups 1-4) compared with the control group receiving separate vaccines, with these differences statistically significant. The difference in rate of fever $\geq$ 38ºC between DTPa-HepB-IPV recipients and the control group ranged from 12.0% to 13.7% after each dose. After any dose, the incidence of fever in DTPa-HepB-IPV recipients was 16.7% more fever than the control group. Of note, the rate of Grade 3 fever was not different between DTPa-HepB-IPV recipients and controls.

Following doses 2 and 3 and after any dose, the rates of restlessness and unusual crying were slightly increased in subjects receiving separate administration of DTPa, Hib and OPV, compared with those receiving DTPa-HepB-IPV and Hib, with these differences statistically significant.

Antipyretic Use

DTPa-HepB-IPV-011 - Percentage of subjects (95%CI) receiving antipyretics within 4 days, for each dose and over the whole vaccination course - ITT cohorts

Group	Dose 1	Dose 2	Dose 3	Any
	% (95%CI)	% (95%CI)	% (95%CI)	% (95%CI)
1	1.1 (0.6 - 1.9)	1.5 (0.9 - 2.3)	1.6 (0.9 - 2.5)	3.8 (2.8 - 5.1)
2	3.9 (2.8 - 5.1)	2.0 (1.3 - 3.0)	1.8 (1.1 - 2.7)	6.3 (5.0 - 7.9)
3	1.2 (0.7 - 2.0)	1.0 (0.5 - 1.7)	1.6 (0.9 - 2.5)	3.4 (2.5 - 4.6)
4	5.5 (4.3 - 7.0)	1.7 (1.0 - 2.6)	2.6 (1.7 - 3.6)	8.1 (6.6 - 9.8)
5	3.6 (2.4 - 5.2)	1.1 (0.5 - 2.1)	0.8 (0.3 - 1.7)	4.9 (3.5 - 6.7)

Group 1: DTPa-HepB-IPV + SB Hib
Group 2: DTPa-HepB-IPV + PM Hib
Group 3: DTPa-HepB-IPV + Led Hib
Group 4: DTPa-HepB-IPV + MSD Hib (Subjects in Group 4 received only 2 doses of Hib vaccine at 3 and 5 months)
Group 5: DTPa + SB Hib + OPV

Reviewer comment: Antipyretic use was low in this study (conducted in Germany) compared with data presented later for Study DTPa-HepB-IPV-015 (conducted in the U.S.) According to SBB, there were no standardized instructions on antipyretic use; however, parents were given similar instructions across studies. Parents were instructed to administer antipyretics if needed. The BLA database did not record whether antipyretic medication was given prophylactically or therapeutically. SBB noted that antipyretic use following vaccination was not a common practice in Germany.

Secondary Endpoint:

Unsolicited symptoms: In the ATP cohort, 1790 (59%) subjects in the pooled DTPa-HBV-IPV vaccine group and 434 (58%) in the control vaccine group reported an unsolicited symptom. Symptoms reported by 48 (1.6%) subjects in the pooled DTPa-HBV-IPV vaccine group and 14 (1.9%) subjects in the control vaccine group were graded 3 in intensity (symptom preventing normal daily activities). Rates of unsolicited symptoms between the pooled DTPa-HBV-IPV vaccine group and the control vaccine group not statistically different (data not shown.)

See Section 3.3.7 for summary data on unsolicited AEs, SAEs and deaths across all studies..

3.3.4 Study DTPa-HB-IPV-015 (U.S. Comparative Safety and Immunogenicity vs. Separately Administered Vaccines)

(See study synopsis provided in section 3.2.3)

Note: Because the ATP cohort excluded less than 1.5% of the enrolled subjects with safety data available, the BLA did not include a reanalysis based on the ITT cohort. Thus, the data presented below are from the ATP cohort for safety. As was noted in section 3.2.3 , review of these data under the BLA focused on groups 1 and 4 because group 2 evaluated a sequential IPV/OPV schedule (no longer the recommended U.S. schedule for polio vaccines) and group 3 evaluated SBB's DTPa-HepB (not licensed in the U.S.)

Safety Objective (secondary objective):

To assess the comparability in terms of safety of DTPa-HepB-IPV co-administered with Hib and the co-administration of DTPa (Infanrix®), hepatitis B vaccine (Engerix-B®), OPV (ORIMUNE®™), and Hib (OmniHIB™), the co-administration of DTPa-HepB, IPV (IPOL ®), and Hib (OmniHIB™), and two consecutive doses of SBB's DTPa-HepB-IPV co-administered with Hib followed by co-administration of DTPa-HepB, OPV and Hib.

Statistical methods:

The overall percentage of subjects with at least one adverse event (local or general, solicited and/or unsolicited), with at least one general adverse event (solicited and/or unsolicited), and with at least one local adverse event during the four-day follow-up period after each vaccination was tabulated and compared between Group 1 and each of the Groups 2, 3, and 4 using the 2-sided Fisher exact test at 5% type I error.

Note: sample size for this study was based on the primary (immunogenicity) endpoints.

Schedule: 2, 4, 6 months

Group 1: DTPa-HB-IPV + Hib at 2, 4, 6 mo
Group 2: DTPa-HB-IPV + Hib at 2, 4 mo; DTPa-HB +Hib + OPV at 6 months
Group 3: DTPa-HB + Hib + IPV at 2, 4, 6 mo
Group 4: DTPa + HB + OPV + Hib at 2, 4, 6 mo

Site of administration

Study DTPa-HepB-IPV-015: Site of Vaccine Administration*			
Group	**Right anterolateral thigh**	**Left anterolateral thigh**	**Oral administration**
1	Hib (OmniHIB™)	DTPa-HepB-IPV	
2	Hib (OmniHIB™)	DTPa-HepB-IPV at 2, 4 mo DTPa-HepB at 6 mo	OPV (ORIMUNE®) at 6 mo
3	Hib (OmniHIB™): upper thigh IPV (IPOL®): lower thigh-SC	DTPa-HepB	
4	Hib (OmniHIB™): upper thigh HepB (Engerix®): lower thigh	Infanrix®	OPV (ORIMUNE®)

*Schedule: 2, 4, 6 months unless otherwise noted

DTPa-HepB-IPV-015: Demographics*

Categories	Total	
	n	%
Total	**332**	
Black	**37**	**11.14**
White	**161**	**48.49**
Asian	**4**	**1.2**
Filipino	**7**	**2.11**
Hispanic	**113**	**34.04**
Indian	**1**	**0.30**
Middle Eastern	**7**	**2.11**
Samoan	**1**	**0.30**
Vietnamese	**1**	**0.30**
Female	**156**	**46.99**
Male	**176**	**53.01**

*ATP cohort for immunogenicity

DTPa-HepB-IPV-015: Incidence of solicited local symptoms following any dose during the 4-day follow-up period per subject: ATP analysis

Symptom	Injection site	Group 1 (N=100)				Group 4 (N=98)				Group 1 minus Group 4		
		n	%	95%CI		n	%	95%CI		Difference	90%CI	
				LL	UL			LL	UL	(%)	LL	UL
Pain	Overall	57	57.0	46.7	66.9	51	52.0	41.7	62.2	5.0	-7.1	17.7
	DTPa-based	55	55.0	44.7	65.0	48	49.0	38.7	59.3	6.0	-6.1	18.9
	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	8.4	-3.1	21.2
	DTPa-based	35	35.0	25.7	45.2	28	28.6	19.9	38.6	6.4	-4.9	19.2
	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	8.4	-2.9	21.2
	DTPa-based	31	31.0	22.1	41.0	20	20.4	12.9	29.7	10.6	-0.4	22.9
	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
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.)

Reviewer comment: This analysis compares local reactogenicity in infants receiving DTPa-HepB-IPV and Hib (group 1) and separately administered DTPa, HepB, Hib and OPV (group 5). When comparing the local reactions occurring at the DTPa-HepB-IPV site with the DTPa site, the incidence of redness was 6.4% greater at the DPTa-HepB-IPV site and the incidence of swelling was 10.6% higher. These differences, however, were not statistically significant. Of note, the sample size of the study was base on immunogenicity endpoints and may have been too small to detect a difference in local symptoms.

As was noted previously in Study-011, it is possible that Study-015 underestimated the incidence of local reactions in the separate vaccine control arm. Group 4 (control group of separately administered vaccines) received OPV rather than IPV which is now the recommended polio regimen. Moreover, in the analysis of overall local symptoms, a symptom was counted only once even if it was reported at multiple sites. Thus, this analysis could not assess any additive local reactogenicity for multiple injection sites.

DTPa-HepB-IPV-015: Incidence of Grade 3 solicited local symptoms following any dose during the 4-day follow-up period per subject: ATP analysis

Symptom	Vaccine	Group 1 (N = 100)				Group 4 (N = 98)			
		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
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.)

DTPa-HepB-IPV-015: Incidence of <u>all solicited general symptoms</u> during the 4-day follow-up period per subject (any dose): ATP cohort

Symptom	Onset	Group 1 N=100				Group 4 N=98				Group 1 minus Group 4		
		n	%	90% CI LL	90% CI UL	n	%	90% CI LL	90% CI UL	Difference %	90% CI LL	90% CI UL
Diarrhea	Onset 2 days	25	25.0	16.9	34.7	25	25.5	17.2	35.3	-0.5	-12.4	11.0
	Total	26	26.0	17.7	35.7	28	28.6	19.9	38.6	-2.6	-14.6	9.1
Fussiness	Onset 2 days	80	80.0	70.8	87.3	81	82.7	73.7	89.6	-2.7	-14.5	7.7
	Total	82	82.0	73.1	89.0	84	85.7	77.2	92.0	-3.7	-15.2	6.2
Loss of appetite	Onset 2 days	36	36.0	26.6	46.2	37	37.8	28.2	48.1	-1.8	-14.1	10.2
	Total	38	38.0	28.5	48.3	38	38.8	29.1	49.2	-0.8	-13.2	11.2
Restlessness	Onset 2 days	37	37.0	27.6	47.2	39	39.8	30.0	50.2	-2.8	-15.2	9.2
	Total	42	42.0	32.2	52.3	42	42.9	32.9	53.3	-0.9	-13.5	11.2
Sleeping more than usual	Onset 2 days	63	63.0	52.8	72.4	57	58.2	47.8	68.1	4.8	-7.2	17.3
	Total	64	64.0	53.8	73.4	59	60.2	49.8	70.0	3.8	-8.2	16.2
Fever (T $\geq$ 38°C)	**Onset 2 days**	**39**	**39.0**	**29.4**	**49.3**	**27**	**27.6**	**19.0**	**37.5**	**11.4**	**0.1**	**24.1**
	Total	41	41.0	31.3	51.3	29	29.6	20.8	39.7	11.4	0.0	24.1
Grade 3 (T > 39.5°C)	Onset 2 days	3	3.0	0.6	8.5	2	2.0	0.2	7.2	1.0	-5.3	8.8
	Total	3	3.0	0.6	8.5	2	2.0	0.2	7.2	1.0	-5.3	8.8
Unusual Crying	Onset 2 days	4	4.0	1.1	9.9	5	5.1	1.7	11.5	-1.1	-9.3	6.7
	Total	6	6.0	2.2	12.6	6	6.1	2.3	12.9	-0.1	-8.8	8.2
Vomiting	Onset 2 days	12	12.0	6.4	20.0	15	15.3	8.8	24.0	-3.3	-13.8	6.8
	Total	13	13.0	7.1	21.2	16	16.3	9.6	25.2	-3.3	-14.0	7.0

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
Onset 2 days = onset of symptoms within 2 days after vaccination
Total = onset of symptoms within the four day follow up period (Day 0-3)

Reviewer comment: As in Study -011, an increased rate of fever (T $\geq$ 38ºC) was observed in subjects receiving DTPa-HepB-IPV compared with separate immunization controls (point estimate of 11.4% with 90% CI 0.1 - 24.1). This difference was statistically significant for onset within two days of vaccination. The difference in rates of Grade 3 fever (T > 39.5ºC) in group 1 minus group 4 was not statistically significant.

Antipyretic Use

DTPa-HepB-IPV-015 - Percentage of subjects (95%CI) receiving antipyretics within 4 days, for each dose and over the whole vaccination course - ATP cohort

Group	Dose 1	Dose 2	Dose 3	Any
	% (95%CI)	% (95%CI)	% (95%CI)	% (95%CI)
1	79.0 (69.7 - 86.5)	67.7 (57.4 - 76.9)	62.1 (51.6 - 71.9)	91.0 (83.6 - 95.8)
4	82.7 (73.7 - 89.6)	70.1 (59.4 - 79.5)	59.5 (48.3 - 70.1)	90.8 (83.3 - 95.7)

Group 1: 3 doses DTPa-HepB-IPV + PMC's Hib
Group 4: DTPa + HepB + PMC's Hib + OPV
% = percentage of subjects who received at least one dose of antipyretics among subjects included in the analysis of solicited fever (95% confidence interval)

Reviewer comment: While a statistical analysis was not performed, the differences in antipyretic use between groups 1 and 4 do not appear to be clinically important. As previously noted, antipyretic use in this U.S. study was significantly higher than in Study –011 conducted in Germany. The rates of fever, however, appear similar both studies. The difference observed in use of antipyretics may reflect different clinical practices in the U.S. and Germany.

Serious Adverse Events: Total of 9 reports in 8 subjects

Group 1: 3 subjects
- Subject 27: Respiratory Syncytial Virus; hospitalized 20 days after 3rd dose
- Subject 298: Seizure disorder, 1st seizure 2 weeks after 1st dose
- Subject 319: Urticarial rash 2 days after 3rd vaccination

Group 2: 3 subjects
- Subject 209: Hospitalized 14 days after 3rd dose for possible apnea
- Subject 215: 2 weeks after 1st dose had onset of weak cry. Diagnosed with neuroblastoma, died 14 months later.
- Subject 276: 5 days after 1st dose, hospitalized to rule out sepsis. Diagnosed with viral syndrome.

Group 3: 1 subject (subject 59): Pneumonia 48 days after 2nd dose.

Group 4: 1 subject (2 reports): Subject 322: Hospitalized for bronchiolitis/right otitis media 27 days after 2nd dose, hospitalized for bronchiolitis 9 days after 3rd dose.

3.3.5 Study DTPa-HB-IPV-044: (Lot-to-lot consistency and manufacturing bridge from 1st to 2nd lot series)

See synopsis provided in Clinical Review Section 3.2.4

Group 1: DTPa-HepB-IPV, Lot A 2nd lot series + Hib (OmniHIB™)
Group 2: DTPa-HepB-IPV, Lot B 2nd lot series + Hib (OmniHIB™)
Group 3: DTPa-HepB-IPV, Lot C 2nd lot series + Hib (OmniHIB™)
Group 4: DTPa-HepB-IPV, 1st lot series + Hib (OmniHIB™)

Safety Objectives (Secondary):

- To evaluate the lot-to-lot consistency in terms of reactogenicity for three production lots of DTPa-HepB-IPV vaccine manufactured according to the new manufacturing process (second lot series).

- To evaluate whether DTPa-HepB-IPV vaccine manufactured according to the new manufacturing

process (second lot series) results in increased reactogenicity as compared to DTPa-HepB-IPV vaccine manufactured according to the initial manufacturing process (first lot series).

Statistical methods (Reactogenicity):

All reactogenicity analyses were exploratory. The difference between the first series (Group 4) and the second series (pooled Groups 1, 2, and 3) in the percentage of subjects experiencing any graded "3" solicited symptom, the percentage of subjects experiencing each solicited symptom, whatever the intensity rating and with intensity rated "3", whatever the dose and the site of vaccination, were calculated with their exact 90% CIs.
For the lot-to-lot consistency of the second series lots, the pairwise differences between Group 1 and Group 2, Group 1 and Group 3, and Group 2 and Group 3 in the percentage of subjects experiencing any grade "3" solicited symptoms during the four-day follow-up period after any of the three doses were evaluated using exact 90% CIs.

Note: Sample size was based on the primary (immunogenicity) endpoints

Demographics*

Characteristics	**Categories**	**Group 1**		**Group 2**		**Group 3**		**Group 4**		**Total**	
		n 107	**%**	**n 112**	**%**	**n 109**	**%**	**n 106**	**%**	**n 434**	**%**
Race	White	92	86.0	101	90.2	93	85.3	94	88.7	380	87.6
	Black	4	3.7	3	2.7	2	1.8	1	0.9	10	2.3
	Asian	1	0.9	0		2	1.8	0		3	0.7
	Other	10	9.4	8	7.1	12	11.0	11	10.4	41	9.5
Gender	Female	40	37.4	52	46.4	56	51.4	54	50.9	202	46.5
	Male	67	62.6	60	53.6	53	48.6	52	49.1	232	53.5

*ATP cohort for immunogenicity

DTPa-HepB-IPV-044: Assessment of Groups 1, 2, and 3 pooled (Second Lot series) and Group 4 (First Lot series) in terms of reactogenicity during the 4-day follow-up period * - ATP cohort (BLA 8.III, Table 4E)

Solicited symptom	Pooled Groups 1, 2, 3		Group 4		Difference Group 4 minus pooled Groups 1, 2, and 3	
	N	Rate (%)	N	Rate (%)	Diff. (%)	90% CI
Any grade "3" solicited symptom	358	18.2	119	15.1	-3.0	[-10.2 ; 4.6]
Local (at injection site)						
Pain	358	49.7	119	49.6	-0.1	[-9.3 ; 8.7]
Pain graded "3"*	358	3.4	119	0.8	-2.5	[-6.0 ; 1.9]
Redness	358	57.5	119	54.6	-2.9	[-12.0 ; 5.9]
Redness > 20 mm	358	4.5	119	2.5	-1.9	[-6.1 ; 3.1]
Swelling	358	39.1	119	37.8	-1.3	[-10.3 ; 7.4]
Swelling > 20 mm	358	3.6	119	5.0	1.4	[-2.9 ; 7.9]
General						
Fever† ≥ 38°C	358	54.7	119	47.9	-6.8	[-15.9 ; 2.0]
Fever† > 39.5°C	358	0.8	119	0.8	0.0	[-2.6 ; 4.9]
Diarrhea	358	32.1	119	33.6	1.5	[-7.0 ; 10.9]
Diarrhea graded "3"***	358	0.6	119	0.0	-0.6	[-2.9 ; 3.1]
Loss of appetite	358	43.6	119	37.8	-5.8	[-14.8 ; 2.9]
Loss of appetite graded "3"***	358	0.6	119	0.8	0.3	[-2.2 ; 5.2]
Fussiness	358	87.7	119	89.1	1.4	[-5.6 ; 8.2]
Fussiness graded "3"**	358	8.4	119	4.2	-4.2	[-9.2 ; 1.6]
Restlessness	358	57.0	119	57.1	0.2	[-8.6 ; 9.8]
Restlessness graded "3"***	358	2.8	119	2.5	-0.3	[-4.1 ; 4.7]
Sleeping more than usual	358	64.5	119	58.0	-6.5	[-15.5 ; 2.3]
Sleeping more than usual graded "3"***	358	2.5	NP	2.5	0.0	[-3.6 ; 5.7]
Vomiting	358	27.1	119	22.7	-4.4	[-12.5 ; 3.8]
Vomiting graded "3"***	358	1.1	119	0.0	-1.1	[-3.7 ; 2.6]

Group 1: DTPa-HBV-IPV, second series Lot A + Hib
Group 2: DTPa-HBV-IPV, second series Lot B + Hib
Group 3: DTPa-HBV-IPV, second series Lot C + Hib
Group 4: DTPa-HBV-IPV, first series + Hib
* grade "3" pain at injection site = cried when the limb was moved/ spontaneously painful (prevented normal everyday activity)
** = Grade "3" irritability/fussiness was described as: Crying** or irritability that could not be comforted.
** Parents were instructed to contact the investigator if the child cried continuously for more than 3 hours.
*** grade "3" = adverse experience preventing normal daily activities (such an adverse experience would, for example, prevent attendance at school/ kindergarten/ a day-care center and would cause the parents/guardians to seek medical advice)
†rectal temperature
N = number of subjects with at least one documented dose
NP=Not provided

Reviewer comment: In this comparison of the first to second lot series, the incidence of fever was 6.8% higher in pooled groups receiving the second lots series compared with the group receiving the first lot series, although this difference was not statistically significant.

3.3.6 Safety of a Primary Series of DTPa-HepB-IPV Following a Birth Dose of Hepatitis B Vaccine

In the studies filed with the BLA, there were no comparative trials examining the use of DTPa-HepB-IPV with and without a birth dose of hepatitis B. The BLA included the supportive study **DTPa-HepB-IPV-030** from Moldova in which all infants received a birth dose of hepatitis B vaccine. Assessment of safety data from this study was further hampered by the inclusion of a combination vaccine containing whole cell pertussis as the comparator to DTPa-HepB-IPV (see Section 3.5.1: Clinical Trial Summary Table for outline of this study).

As an amendment to the BLA, SBB submitted the complete study report of study DTPa-HepB-IPV/Hib-003 to provide supportive data (BLA amendment 11/3/00). This study compared a primary series at 2, 4, 6 months of age of SBB's DTPa-HepB-IPV/Hib product (DTPa-HepB-IPV mixed extemporaneously with SBB's Hib [PRP-T] prior to injection) following a birth dose of hepatitis B vaccine, with a primary series of DTPa-HepB-IPV/Hib given without a birth dose. Monitoring for adverse events was performed as in previously described studies of DTPa-HepB-IPV.

DTPa-HepB-IPV/Hib-003: Supportive study

Title: A phase III open randomized multicenter controlled study of the safety and immunogenicity of three doses of SBB's DTPa-HBV-IPV/Hib vaccine administered at 2, 4 and 6 months of age following a birth dose of Engerix-B ® compared to three doses of SBB's DTPa-HBV-IPV/Hib vaccine administered at 2, 4 and 6 months of age without a birth dose of hepatitis B vaccine.

Location: USA

Schedule: 2, 4, 6 months

Study Design: open, randomized, multicenter

Group 1: DTPa-HepB-IPV/Hib without birth dose of hepatitis B
Group 2: DTPa-HepB-IPV/Hib with birth dose of hepatitis B

Number of subjects enrolled (ITT cohort): 550 (275 each group)
ATP cohort for safety: 525
- Group 1: 259
- Group 2: 266

ATP cohort for immunogenicity: 170
- Group 1: 84
- Group 2: 86

Note: Because the ATP cohort excluded less than 1.5% of the enrolled subjects with safety data available, the BLA did not include a reanalysis based on the ITT cohort. Thus, the data presented below are from the ATP cohort for safety.

Study DTP-HepB-IPV/Hib-003: "Grade 3" solicited symptoms during the 8-day follow-up period after any of the 3 DTPa-HepB-IPV/Hib doses

Symptom	Group 1		Group 2		Difference (Group 2 minus Group 1)		
					Diff.	90% CI	
	N	%	N	%	(%)	LL	UL
Any "grade 3" solicited symptoms‡	259	23.2	265	22.6	-0.5	-7.4	6.1*
"Grade 3" pain at injection site	259	3.9	265	4.5	0.7	-3.1	5.0
Redness >20 mm at injection site	259	5.4	265	3.0	-2.4	-6.6	1.5
Swelling >20 mm at injection site	259	7.7	265	3.8	-3.9	-8.6	0.3
"Grade 3" fever (>39.5°C)	259	0.4	265	2.6	2.3	-0.3	5.7
"Grade 3" drowsiness	259	4.6	265	4.2	-0.5	-7.4	6.1
"Grade 3" irritability/fussiness	259	9.7	265	13.6	3.9	-1.3	9.7
"Grade 3" loss of appetite	259	2.3	265	0.4	-1.9	-5.1	0.8

Group 1: without birth dose hepatitis B vaccine
Group 2: with birth dose of hepatitis B vaccine
N = number of subjects with at least one symptom sheet completed
% = percentage of subjects reporting the specific symptom during the 8-day follow-up period after any vaccination
‡ = primary endpoint
* = upper 90% CI limit below the 7.5% clinical limit for non-inferiority (defined only for the primary endpoint)

Reviewer comment: With respect to the primary endpoint of any grade 3 solicited symptoms, DTPa-HepB-IPV/Hib administered following a birth dose of hepatitis B was shown to be within the prespecified limits of non-inferiority when compared with DTPa-HepB-IPV/Hib administered without a birth dose of hepatitis B. With respect to specific grade 3 solicited symptoms, fever (>39.5°C) was increased in the group receiving the birth dose, but this difference was not statistically significant.

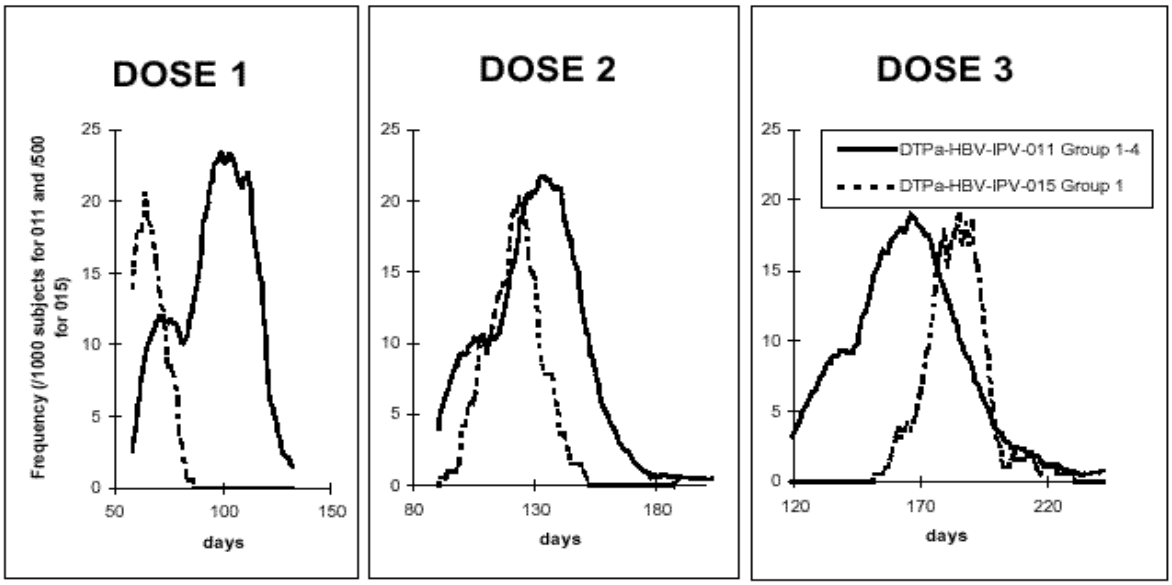
3.3.7 Summary Safety Data

A. Bridging Between 3, 4, 5 month schedule and 2, 4, 6 month schedule

SBB submitted data to support comparability of safety data obtained on a 3, 4, 5 month schedule in Germany (DTPa-HepB-IPV-011) with that obtained on a 2, 4, 6 month schedule (DTPa-HepB-IPV-015 and –044). This comparison was sought to determine whether the safety profile of DTPa-HepB-IPV was similar for infants administered under the 3, 4, 5 month regimen in which the first dose was administered approximately one month later and the schedule was more compressed when compared to the 2, 4, 6 month schedule. Of note, study designs and subject monitoring were similar across the studies (see Section 3.3.2-3.5.5). To examine this issue, SBB provided a comparison of the age distribution for each dose and examined the incidence of solicited symptoms under the two schedules.

The following figure compares the age distribution of the subjects for each dose between the Studies –011 and –015. The age of enrollment for Study –011 was 8-16 weeks; for studies –015 and –044 the allowable age of enrollment was 6-12 weeks.

Comparison of the age distribution (relative number of subjects per age in days) at each dose for the groups who received three consecutive doses of DTPa- HepB- IPV vaccine in study 011 (Germany- schedule 3, 4, 5) and in study 015 (US- schedule 2, 4, 6) (BLA, Figure 8.II. 9- 1)



Reviewer comment: Study DTPa-HepB-IPV-011 utilized a 3, 4, 5 month schedule while Study –015 used a 2, 4 , 6 month schedule. The age at the time of vaccination overlapped between the two studies, with the timing of the second dose most similar.

The percentage of subjects with solicited local symptoms (any grade and by dose) and over the full vaccination course - ATP safety cohort (BLA Table 8. II. 9- 6)

Local Solicited Symptoms	DTPa-HepB-IPV-011				DTPa-HepB-IPV-015			
	Groups 1-4 DTPa-HepB-IPV+Hib		Control DTPa+Hib+OPV		Group 1 DTPa-HepB-IPV+Hib		Control DTPa+HepB+Hib+OPV	
	Any	Grade 3	Any	Grade 3	Any	Grade 3	Any	Grade 3
	% (LL-UL)	% (LL-UL)	% (LL-UL)	% (LL-UL)	% (LL.-UL)	% (LL-UL)	% (LL-UL)	% (LL-UL)
Dose 1								
Pain	16.7(15.3-18.1)	1.4 (1.0-1.8)	20.7(17.8-23.8)	3.0 (1.9-4.4)	38.0 (28.5-48.3)	3.0 (0.6-8.5)	38.8 29.1-49.2)	4.1 (1.1-10.1)
Redness	23.8(22.3-25.4)	2.3 (1.8-2.9)	24.7(21.7-28.0)	6.2 (4.6-8.2)	18.0 (11.0-26.9)	2.0 (0.2-7.0)	17.3 10.4-26.3)	0.0 (0.0-3.7)
Swelling	17.2 (15.9-18.6)	1.8 (1.4-2.4)	16.5(13.9-19.4)	3.0 (1.9-4.4)	12.0 (6.4-20.0)	2.0 (0.2-7.0)	11.2 (5.7-19.2)	2.0 (0.2-7.2)
Dose 2								
Pain	11.3 (10.2-12.5)	0.4 (0.2-0.7)	11.5(9.3-14.0)	0.5 (0.1-1.4)	28.1 (19.4-38.2)	0.0 (0.0-3.8)	20.7(12.7-30.7)	0.0 (0.0-4.2)
Redness	29.0 (27.4-30.6)	1.2 (0.9-1.7)	26.2(23.0-29.5)	1.4 (0.7-2.5)	18.8 (11.5-28.0)	1.0 (0.0-5.7)	12.6 (6.5-21.5)	0.0 (0.0-4.2)
Swelling	21.0 (19.5-22.5)	2.0 (1.5-2.5)	15.3(12.8-18.1)	1.8 (0.9-3.0)	17.7 (10.7-26.8)	2.1 (0.3-7.3)	14.9 (8.2-24.2)	2.1 (0.0-6.2)
Dose 3								
Pain	11.4 (10.3-12.6)	0.4 (0.2-0.7)	9.7(7.7-12.1)	0.4 (0.1-1.2)	22.1 (14.2-31.8)	0.0 (0.0-3.8)	22.6(14.2-33.0)	1.2 (0.0-6.5)
Redness	29.1 (27.5-30.8)	1.4 (1.0-1.9)	25.3(22.2-28.6)	1.6 (0.9-2.8)	23.2 (15.1-32.9)	0.0 (0.0-3.8)	14.3 (7.6-23.6)	1.2 (0.0-6.5)
Swelling	21.1 (19.6-22.6)	1.7 (1.3-2.3)	17.2(14.6-20.2)	1.6 (0.9-2.8)	17.9 (10.8-27.1)	2.1 (0.3-7.4)	11.9 (5.9-20.8)	1.2 (0.0-6.5)
Overall								
Pain	26.5 (25.0-28.2)	2.0 (1.5-2.5)	28.4(25.1-31.7)	3.6 (2.4-5.2)	57.0 (46.7-66.9)	3.0 (0.6-8.5)	52.0(41.7-62.2)	5.1 (1.7-11.5)
Redness	46.3 (44.5-48.0)	4.2 (3.5-5.0)	45.6(41.9-49.2)	8.3 (6.4-10.6)	40.0 (30.3-50.3)	3.0 (0.6-8.5)	31.6(22.6-41.8)	1.0 (0.0-5.6)
Swelling	35.9 (34.2-37.7)	4.1 (3.4-4.9)	33.2(29.8-36.7)	5.0 (3.5-6.8)	36.0 (26.6-46.2)	6.0 (2.2-12.6)	27.6(19.0-37.5)	3.1 (0.6-8.7)

Comparison of subjects with solicited general symptoms in study DTPa-HepB-IPV-011 (3, 4, 5 month schedule) and DTPa-HepB-IPV-015 (2, 4, 6 month schedule (ATP cohort for safety) (Adapted from Table 8. II. 9- 7)

General Solicited Symptoms	DTPa-HepB-IPV-011		DTPa-HepB-IPV-015	
	Groups 1-4 DTPa-HepB-IPV+Hib	Group 5-Control DTPa+Hib+OPV	Group 1 DTPa-HepB-IPV+Hib	Group 4- Control DTPa+HepB+Hib+OPV
	%(LL-UL)	% (LL-UL)	% (LL-UL)	% (LL-UL)
Dose 1				
Loss of appetite	17.8 (16.4-19.2)	19.5 (16.7-22.5)	25.0 (16.9-34.7)	23.5 (15.5-33.1)
Restlessness	42.8 (41.0-44.6)	46.4 (42.7-50.0)	62.0 (51.7-71.5)	63.3 (52.9-72.8)
Fever (T≥ 38°C)	22.6 (21.1-24.2)	13.4 (11.1-16.1)	23.0 (15.2-32.5)	15.3 (8.8-24.0)
Unusual crying	25.6 (24.0-27.2)	36.6 (33.1-40.1)	2.0 (0.2-7.0)	3.1 (0.6-8.7)
Vomiting	9.7 (8.6-10.8)	12.0 (9.7-14.5)	9.0 (4.2-16.4)	10.2 (5.0-18.0)
Dose 2				
Loss of appetite	14.0 (12.7-15.2)	16.3 (13.7-19.1)	16.7 (9.8-25.6)	13.8 (7.3-22.9)
Restlessness	33.2 (31.5-34.9)	34.7 (31.3-38.2)	55.2 (44.7-65.4)	48.3 (37.4-59.2)
Fever (T≥ 38°C)	18.2 (16.8-19.6)	13.3 (10.9-15.9)	17.7 (10.7-26.8)	13.8 (7.3-22.9)
Unusual crying	17.5 (16.2-18.9)	19.9 (17.1-23.0)	3.1 (0.6-8.9)	1.1 (0.0-6.2)
Vomiting	7.5 (6.5-8.5)	8.4 (6.5-10.6)	4.2 (1.1-10.3)	8.0 (3.3-15.9)
Dose 3				
Loss of appetite	12.5 (11.3-13.8)	11.2 (9.0-13.7)	12.6 (6.7-21.0)	16.7 (9.4-26.4)
Restlessness	27.0 (25.4-28.6)	27.5 (24.3-30.9)	47.4 (37.0-57.9)	48.8 (37.7-60.0)
Fever (T ≥ 38°C)	19.1 (17.7-20.5)	11.2 (9.0-13.7)	16.8 (9.9-25.9)	13.1 (6.7-22.2)
Unusual crying	13.4 (1.2-14.7)	14.2 (11.8-17.0)	1.1 (0.0-5.7)	2.4 (0.3-8.3)
Vomiting	5.6 (4.8-6.5)	5.2 (3.7-7.1)	2.1 (0.3-7.4)	4.8 (1.3-11.7)
Overall				
Loss of appetite	31.6 (29.9-33.3)	33.9 (30.5-37.4)	38.0 (28.5-48.3)	38.8 (29.1-49.2)
Restlessness	59.6 (57.8-61.3)	61.8 (58.2-65.3)	82.0 (73.1-89.0)	85.7(77.2-92.0)
Fever (T≥ 38°C)	40.6 (38.9-42.4)	27.0 (23.9-30.4)	41.0 (31.3-51.3)	29.6(20.8-39.7)
Unusual crying	39.2 (37.5-41.0)	48.9 (45.3-52.6)	6.0 (2.2-12.6)	6.1 (2.3-12.9)
Vomiting	17.2 (15.8-18.6)	19.6 (16.8-22.7)	13.0 (7.1-21.2)	16.3 (9.6-25.2)

Comparison of subjects with solicited grade 3 general symptoms in study DTPa-HepB-IPV-011 (3, 4, 5 month schedule) and DTPa-HepB-IPV-015 (2, 4, 6 month schedule) (ATP cohort for safety) (Adapted from Table 8. II. 9- 7)

General Solicited Symptoms	DTPa-HepB-IPV-011		DTPa-HepB-IPV-015	
	Groups 1-4 DTPa-HepB-IPV+Hib	Group 5-Control DTPa+Hib+OPV	Group 1 DTPa-HepB-IPV+Hib	Group 4- Control DTPa+HepB+Hib+OPV
	Grade 3 % (LL-UL)	Grade 3 % (LL-UL)	Grade 3 % (LL-UL)	Grade 3 % (LL-UL)
Dose 1				
Loss of appetite	0.6 (0.4-1.0)	0.5 (0.1-1.4)	0.0 (0.0-3.6)	1.0 (0.0-5.6)
Restlessness	2.6 (2.1-3.3)	5.6 (4.1-7.6)	2.0 (0.2-7.0)	4.1(1.1-10.1)
Fever	0.3 (0.1-0.5)	0.1 (0.0-0.7)	1.0 (0.0-5.4)	0.0 (0.0-3.7)
Unusual crying	3.8 (3.1-4.5)	6.5 (4.8-8.5)	0.0 (0.0-3.6)	0.0 (0.0-3.7)
Vomiting	0.2 (0.1-0.5)	0.0 (0.0-0.5)	0.0 (0.0-3.6)	1.1 (0.0-5.6)
Dose 2				
Loss of appetite	0.6 (0.4-1.0)	0.7 (0.2-1.6)	1.0 (0.0-5.7)	1.1 (0.0-6.2)
Restlessness	1.5 (1.1-2.0)	3.0 (1.9-4.5)	3.1 (0.6-8.9)	4.6(1.3-11.4)
Fever	0.5 (0.3-0.8)	0.1 (0.0-0.8)	1.0 (0.0-5.7)	2.3 (0.3-8.1)
Unusual crying	1.7 (1.3-2.3)	2.0 (1.1-3.3)	0.0 (0.0-3.8)	0.0 (0.0-4.2)
Vomiting	0.4 (0.2-0.7)	0.5 (0.1-1.4)	1.0 (0.0-5.7)	1.1 (0.0-6.2)
Dose 3				
Loss of appetite	0.5 (0.3-0.8)	0.0 (0.0-0.5)	0.0 (0.0-3.8)	0.0 (0.0-4.3)
Restlessness	1.5 (1.1-2.0)	1.8 (1.0-3.0)	3.2 (0.7-9.0)	4.8(1.3-11.7)
Fever	0.8 (0.5-1.2)	0.5 (0.1-1.4)	1.1 (0.0-5.7)	0.0 (0.0-4.3)
Unusual crying	1.5 (1.1-2.0)	1.1 (0.5-2.1)	0.0 (0.0-3.8)	0.0 (0.0-4.3)
Vomiting	0.5 (0.3-0.9)	0.1 (0.0-0.8)	0.0 (0.0-3.8)	0.0(0.0-4.3)
Overall				
Loss of appetite	1.5 (1.1-2.0)	1.1 (0.5-2.1)	1.0 (0.0-5.4)	2.0(0.2-7.2)
Restlessness	5.1 (4.3-5.9)	8.6(6.7-10.9)	7.0 (2.9-13.9)	11.2(5.7-19.2)
Fever	1.4 (1.0-1.9)	0.8 (0.3-1.7)	3.0 (0.6-8.5)	2.0(0.2-7.2)
Unusual crying	6.0 (5.2-6.9)	8.9(6.9-11.1)	0.0 (0.0-3.6)	0(0.0-3.7)
Vomiting	1.1 (0.7-1.5)	0.7 (0.2-1.6)	1.0 (0.0-5.4)	2.0(0.2-7.2)

Note - The analyses presented in the preceding 3 tables examined the ATP cohorts for safety, therefore figures may be different from that presented in section 3.3.3 for Study -011.)

Reviewer comment: The previous three tables compared the observed rates of local and general symptoms between infants in study DTPa-HepB-IPV-011 (3, 4, 5 month schedule in Germany) and DTPa-HepB-IPV-015 (2, 4, 6 month schedule in the U.S.)

Similar trends were seen in each group, with overall fever $\geq$ 38°C occurring in DTPa-HepB-IPV recipients in approximately 40% of subjects in both studies.

Some differences were observed in the incidence of local and general solicited symptoms when comparing the vaccine schedules. For local symptoms, the incidence of “any pain” was higher in the U.S. population. For general symptoms, the incidence of “unusual crying” was higher in the German population, while the incidence of restlessness" was higher in the US population. When comparing Grade 3 symptoms, the rates of both local and general symptoms appeared similar in the two studies.

Given the overlap in age of vaccination for each dose and the overall similarities in local symptom rates, it appears reasonable to consider the 3, 4, 5 months schedule comparable to the 2, 4, 6 months schedule with respect to the safety profile for solicited adverse events.

B. Table: Incidence of Unsolicited Adverse Events – Subjects Receiving DTPa-HepB-IPV Compared with Separately Administered U.S. Licensed Vaccines (Data to be available at VRPBAC)

C. Narrative summary of subjects across all studies reported to have experienced Serious Adverse Events "SAEs" considered to be related to vaccination (Directly from BLA 8.II.5.2.1)

DTPa-HepB-IPV-011: Subject no. 5390, a 2½ month-old male with a past medical history of vomiting, received the first dose of DTPa-HepB-IPV and PM Hib vaccines simultaneously at separate sites. Approximately 30 minutes after vaccination, the child began to cry and was noted to have pain, redness, and swelling at the Hib vaccine injection site. The crying continued for several hours and eventually resolved later that day following administration of medication. Two more episodes of crying lasting approximately two hours each were noted, one on the day of vaccination and the other on the following day. The investigator stated that the event was a significant side effect, which was *related* to study vaccination. The child received his second and third doses of DTPa-HepB-IPV and PM Hib vaccines uneventfully.

DTPa-HepB-IPV-011: Subject no. 6811, a 2 month-old male, received his first dose of DTPa-HepB-IPV and Merck Hib vaccines simultaneously at separate sites. Approximately five hours later, the child developed restlessness, fever, and severe pain on pressure at the Hib injection site associated with redness of the whole outer thigh. He recovered completely the next day. The investigator stated that these events were *related* to the study vaccination and that the local events were *related* to the Hib vaccination. The child completed the vaccination course.

DTPa-HepB-IPV-011: Subject no. 7321, a 3 month-old male, developed a high fever (39.0°C/102.2°F) beginning two days after the second dose of DTPa-HepB-IPV and Merck Hib vaccines simultaneously at separate sites. He continued to have a fever for the next two days which increased to 41.0°C/105.8°F associated with restlessness and sleeping more than usual. The investigator stated that the event was *definitely related* to the study vaccination. The child recovered; however, the vaccination course was discontinued.

SAEs considered to be possibly related to vaccination:

DTPa-HepB-IPV-011: Subject no. 133, a 6 month-old male, received the second dose of DTPa-HepB-IPV vaccine and Lederle Hib vaccine simultaneously at separate sites. In the evening, the child experienced a change in behavior associated with a fever (rectal temperature up to 40.0°C/104.0°F. Three days later, he was given an antipyretic and approximately one hour later, he vomited and became hypotonic. He was hospitalized and treated with diazepam: On admission, he was agitated and febrile (39.7°C/103.5°F).Lab tests and EEG were within normal limits. He was treated with intravenous fluids, the fever resolved, and no convulsions were observed. After two days, the child recovered and was discharged. Of note, the child reportedly had rhinitis and purulent conjunctivitis for several days prior to vaccination. The investigator stated that the events were *possibly relate*d to study vaccination but they could also be associated with a suspected influenza infection. The vaccination course was discontinued for this child since he was withdrawn from the study by his parents. . *[Reviewer comment:* It is not clear from the available information whether seizures were diagnosed in this infant.]

DTPa-HepB-IPV-011: Subject no. 4926, a 5½ month-old female, developed fever and tachycardia one day after administration of the third dose of DTPa-HepB-IPV vaccine and PM Hib vaccine simultaneously at separate sites. The child was hospitalized and on admission was found to have regular cardiac rhythm, fever and rhinitis without evidence of cardiac failure, cyanosis, pathologic cardiac murmur, or exanthema. She continued to have a fever (rectal temperature of 39.9°C/103.8°F) with elevated heart rate (145-200/min) for the next two days and was treated with intravenous fluid and antipyretics. Four days post-vaccination she was discharged with a diagnosis of possible viral infection with tachycardia secondary to fever; however, the investigator could not rule out a *possible associatio*n with study vaccination.

D. Hospitalizations (All BLA Studies)

A total of 173 subjects were hospitalized across all clinical studies included in the BLA.

Number of subjects reporting SAEs resulting in hospitalization by vaccine administered (Adapted from BLA amendment 3/3/00, Table 63-1)

Dose number	Any Vaccine	DTPa-HepB-IPV N=7028 (rate)	Comparator Vaccine N=1764 (rate)
1	68	61 (0.87%)	7 (0.40%)
2	46	34 (0.48%)	12 (0.68%)
3	53	42 (0.60%)	11 (0.62%)
More than one dose*	7	6 (0.085%)	1 (0.057%)
TOTAL	173	142 (2.0%)	31 (1.8%)

*7 subjects were hospitalized following more than one dose during the study period.

The overall rates of hospitalization were similar for DTPa-HepB-IPV vaccine and comparator vaccine recipients (2.0% and 1.8%, respectively). For the DTPa-HepB-IPV vaccine group, more reports were received after the first dose than after subsequent doses.

G. Deaths (All BLA Studies)

6 deaths reported during course of 12 BLA trials (BLA 8.II.7)

DTPa-HepB-IPV:
5 deaths; N=7028
Cause of death: 2 SIDS, 1 convulsive disorder, 1 congenital immunodeficiency with sepsis, 1 neuroblastoma)

Control regimens:
1 death; N=1,764
Cause of death: 1 SIDS

Narrative summary of deaths in all BLA studies:

Study 011: 4 total: 3 (DTPa-HepB-IPV); 1 (Control)

DTPa-HepB-IPV: Subject 1030: Seizures associated with T 38.3^{o}C 4 days after 1st vaccination. Subsequent afebrile seizures. Evaluation including CSF, stool, serology, head sonogram and MRI normal. Found dead in crib 4 weeks later, clinically felt to be related to seizure disorder. Parents refused autopsy.

DTPa-HepB-IPV: Subject 1377: Past medical history significant for preterm birth (BW 1490 g), apnea on aminophylline, cerebral bleeding, transitional hypoparathyroidism. 23 days after 3rd vaccination, child had febrile convulsion. Hospitalized, died a few days later. Autopsy dx of "congenital deficiency immunopathy."

DTPa-HepB-IPV: Subject 6860: 18 days after 2nd vaccination died of SIDS. No further details. No autopsy.

Control (DTaP+HepB+OPV): Subject 6208: Previously healthy, 21 days after 2nd vaccination he was found dead. Clinical dx SIDS. Parents refused autopsy.

Study 002:

DTPa-HepB-IPV: SIDS death in 10 week old infant 4 days after 1st vaccination. Autopsy consistent with SIDS. No fever or local reactions; cried > 1 hr after vaccination**.**

Study 015:

DTPa-HepB-IPV: 2 month old infant, 2 weeks after first vaccination had onset of progressively weak cry, decreased po intake, decreased motor activity. 1 1/2 months after vaccination had quadriparesis. MRI and CT revealed neuroblastoma. The infant died 1 year later.

3.4 Safety and Immunogenicity of DTPa-HepB-IPV with Concurrent Immunizations

3.4.1 DTPa-HepB-IPV administered concurrently with *Haemophilus influenzae* type (Hib) vaccine

Concurrent Hib vaccine was administered in BLA studies DTPa-HepB-IPV-002, -004, -011, -012, -015, -016,- 017, -030, and –044. Each study included evaluation of both safety and immunogenicity, with exception of DTPa-HepB-IPV-011 which included only safety endpoints. Comparative data on the immune responses to Hib vaccine when DTPa-HepB-IPV was concurrently administered with Hib compared with immunization with separate injections of DTPa, hepatitis B, IPV, and Hib vaccine were obtained in DTPa-HepB-IPv-012 and DTPa-HepB-IPV-015 (see table below).

Comparative safety data on DTPa-HepB-IPV given concomitantly with Hib vaccines from different manufacturers were obtained in studies DTPa-HepB-IPV-011 (U.S.) and DTPa-HepB-IPV-012 (Lithuania).

A. DTPa-HepB-IPV administered concurrently with Hib vaccine: Immunogenicity data

Summary across all BLA studies: Immune response to PRP one month after primary vaccination with Hib vaccine and SBB DTPa- HepB- IPV vaccine administered separately (BLA Table 8. III. 1- 23)

Study	Hib vaccine	Lab	N	Anti-PRP				
				0.15 mcg/ml		1.0 mcg/ml		GMT (mcg/ml)
				%	[95% CI]	%	[95% CI]	[95% CI]
2-4-6 months								
DTPa-HepB-IPV-002	Lederle Hib	SBB	25	91.3	NC	NC	NC	1.9 [NC]
DTPa-HepB-IPV-004	PM Hib	SBB	46	97.8	[87.0–99.9]	89.1	[75.6–95.9]	6.3 [4.0–9.8]
DTPa-HepB-IPV-015	PM Hib	MEP	90	98.9	[94.0–100]	94.4	[87.5–98.2]	6.2 [4.9 – 7.8]
DTPa-HepB-IPV-044*	PM Hib	MEP	328	100	[98.9–100]	90.9	[87.2–93.7]	5.5 [4.8–6.2]
DTPa-HepB-IPV-044†	PM Hib	MEP	106	100	[96.6–100]	91.5	[84.5–96.0]	6.8 [5.4–8.6]
3-4-5 months								
DTPa-HepB-IPV-005	SBB Hib	SBB	343	98.8	[96.8–99.6]	92.7	[89.3–95.1]	5.5 [4.8–6.3]
DTPa-HepB-IPV-016	SBB Hib	MEP	161	98.1	[94.7–99.6]	88.2	[82.2–92.7]	5.6 [4.5–7.0]
3-4.5-6 months								
DTPa-HepB-IPV-012	SBB Hib	SBB	202	100	[97.7–100]	96.0	[92.1–98.1]	7.2 [6.2–8.3]
	PM Hib	SBB	101	99.0	[93.8–99.9]	94.1	[87.0–97.6]	6.7[5.4–8.2]
	Lederle Hib	SBB	100	100	[95.4–100]	88.0	[79.6–93.4]	5.8 [4.4–7.5]
	Merck Hib‡	SBB	105	100	[95.6–100]	90.5	[82.8–95.1]	5.0 [4.0–6.1]
2-3-4 months								
DTPa-HepB-IPV-017	SBB Hib	MEP	23	100	[82.2–100]	73.9	[51.3–88.9]	3.2 [1.6–6.3]
1.5-2.5-3.5 months								
DTPa-HepB-IPV-030§	SBB Hib	MEP	150	96.0	[91.5–98.5]	65.3	[57.1–72.9]	1.9 [1.5–2.4]

N=Number of subjects %= percentage of subjects the specified titer

*One of three second lot series administered concomitantly

†One First Lot Series lot (lot 21710A2) administered concomitantly

‡Subjects received only 2 doses of Merck Hib vaccine at 3 and 6 months

§HepB vaccine at birth

N. B.: Data not always directly comparable due to differences in methodology

DTPa-HepB-IPV-012 & DTPa-HepB-IPV-015: Immunogenicity of Hib vaccine administered concurrently (at separate sites) with DTPa-HepB-IPV compared with separate administration of DTPa, hepatitis B, IPV, and Hib vaccines

Study/Location (schedule)	Group	N	% 0.15 mcg/ml		% 1.0 mcg/ml		GMT (mcg/ml)	
				[95 % CI]		[95 % CI]		[95 % CI]
DTPa-HepB-IPV-012/ Lithuania (3, 4.5, 6 m)	Group 1	202	100	[97.7–100]	96.0	[92.1–98.1]	7.2	[6.2–8.3]
	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/ U.S. (2, 4, 6m)	Group 1	90	98.9	[94.0–100]	94.4	[87.5–98.2]	6.2	[4.9–7.8]
	Group 4	78	100	[95.4–100]	94.9	[87.4–98.6]	7.8	[6.1–10.1]

DTPa-HepB-IPV-012:
Group 1 - SBB DTPa-HepB-IPV + SBB Hib
Group 2 - SBB DTPa-HepB-IPV + PM 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
DTPa-HepB-IPV-015:
Group 1 – SBB DTPa-HepB-IPV + PM Hib
Group 4 – SBB DTPa + SBB HepB + Lederle OPV + PM Hib
N = Number of subjects
% = Percentage of subjects

Reviewer Comment: No significant differences were observed in immune responses to Hib vaccine when DTPa-HepB-IPV was concurrently administered with Hib compared with immunization with separate injections.

B. DTPa-HepB-IPV administered concurrently with Hib vaccine: Safety data

In all three pivotal studies, infants in each group received concurrent Hib vaccine. See sections 3.3.3-3.3.5 for safety data.

3.4.2 DTPa-HepB-IPV administered concurrently with pneumococcal conjugate vaccine (Prevnar)

No data have been submitted to the FDA to date evaluating DTPa-HepB-IPV with concurrent Prevnar, Wyeth-Lederle's 7-valent pneumococcal conjugate vaccine. This product was not licensed until February 2000, after submission of the DTPa-HepB-IPV BLA in July 1999.

Although no data are available evaluating concurrent DTPa-HepB-IPV and Prevnar, data submitted to the FDA under PLA 99-0279 (Pneumococcal 7-valent Conjugate Vaccine [Diphtheria$_{197}$ CRM] Protein [Prevnar™]) have suggested that concurrent administration of Prevnar with DTPa or DTPa combination vaccines may affect both immunogenicity and reactogenicity. (See Appendix 1).

3.5 4th Dose DTPa (Infanrix®) following a primary series of DTPa-HepB-IPV

While not formally considered a part of this BLA, SBB submitted summary safety and immunogenicity data on 4th (toddler) dose of Infanrix® or Infanrix®-based combinations following a primary series with DTPa-HepB-IPV. Only one of these studies (DTPa-HepB-IPV-015B) compared the safety and immunogenicity of a booster dose of separately administered Infanrix® and Hib vaccine in children who received a primary series of DTPa-HepB-IPV versus separate injections of DTPa + hepatitis B + OPV. Those data are found in Appendix 2.

4.0 Summary of Available Data Under Consideration for BLA

Objective	Data	Study No.	
		Pivotal	Supportive
Primary series in infants	Safety/Immunogenicity	DTPa-HepB-IPV-011 (Safety Only), -015, -044	DTPa-HepB-IPV-001, -002, -004, -005, -012, -016, -017, -019, -030
Lot consistency	Safety/Immunogenicity	DTPa-HepB-IPV-044	DTPa-HepB-IPV-005 DTPa-HepB-IPB/Hib-027
Clinical bridge for manufacturing change (1st to 2nd lot series)	Safety/Immunogenicity	DTPa-HepB-IPV-044	--
Concurrent vaccination with Hib	Safety/Immunogenicity	DTPa-HepB-IPV-015	DTPa-HepB-IPV-012, -002, -004, -011, -016, -017, -030
Hepatitis B schedule change	Safety/Immunogenicity	--	DTPa-HepB-030
DTPa-HepB-IPV at 2, 4, 6 months following a birth dose of hepatitis B	Safety/Immunogenicity	--	DTPa-HepB-IPV/Hib-003 DTPa-HepB-IPV-030
4th dose DTPa (Infanrix®) booster following primary series with DTPa-HepB-IPV at 2, 4, 6 months of age	Safety/Immunogenicity	--	DTPa-HepB-IPV-015B, -028, -061(booster to –044)

Data Not Submitted in BLA: Concurrent vaccination with Prevnar (7vPnC); use in infants born to hepatitis B surface antigen positive mothers; concurrent administration with MMR and varicella vaccines; fifth dose (4-6 yrs) Infanrix® DTPa following primary series of DTPa-HepB-IPV; and safety and immunogenicity in former preterm infants.

Appendix 1: Concurrent Immunization of Prevnar and DTPa or DTPa-combination

Although no data are available evaluating concurrent DTPa-HepB-IPV and Prevnar (Wyeth-Lederle's 7-valent pneumococcal conjugate vaccine), data submitted to the FDA under PLA 99-0279 (Pneumococcal 7-valent Conjugate Vaccine [Diphtheria$_{197}$ CRM] Protein [Prevnar™]) have suggested that concurrent administration of Prevnar with either of two DTPa vaccines may affect both immunogenicity and reactogenicity endpoints.

Specifically, data from prelicensure studies of Prevnar demonstrated decreased immune response to certain pertussis components and increased fever (>38.0°C) when Prevnar was given concurrently with Wyeth-Lederle's DTPa vaccine (Acel-Imune) (see Appendix 6, Prevnar package insert Tables 5, 6, 10, and 11). In addition, Study 118-503, conducted in Germany on a 3, 4, 5 month schedule under a post-licensure commitment between the FDA and Wyeth-Lederle, evaluated the immunogenicity and reactogenicity of SBB's DTPa-IPV/Hib administered concurrently with Prevnar. SBB's DTPa-IPV/Hib vaccine consists of the same DTPa (Infanrix®) and IPV components as in SBB's DTPa-HepB-IPV, and contains SBB's PRP-T vaccine. As was found with concurrent administration of Prevnar with Acel-Immune, this study demonstrated decreased immune response to certain pertussis components and increased fever (>38.0°C) when Prevnar was administered concurrently with DTPa-IPV/Hib (see study synopsis below).

Wyeth-Lederle Post-marketing Study

Title: Multicenter, randomized study evaluating the safety, immunogenicity and reactogenicity of Wyeth-Lederle's 7-valent Pneumococcal Conjugate Vaccine (7VPnC) concurrently administered to SBB's DTPa-IPV/Hib vaccine compared to administration of DTPa-IPV/Hib only, for the infant immunization series at 3, 4, and 5 month of age

Location: Germany

Products: Wyeth-Lederle's Prevnar and SBB's DTPa-IPV/Hib
(Concurrent hepatitis B was permitted with the study vaccines, Subjects who received hepatitis B (N=83) were evenly divided between the Prevnar group and the control group.)

Sponsor: Lederle-Arzneimittel GmbH (on behalf of Wyeth-Lederle Vaccines)

Study Site: Twelve study centers in Germany

Status: Study described as ongoing at the time of the report.

Total planned:	200	
Total enrolled:	231	
Analyzed for Safety:	231	
Analyzed for Immunogenicity (ITT):		223
Analyzed for Immunogenicity (ATP):		158

Objective: To show that Prevnar administered with DTPa-IPV/Hib does not diminish the immunogenicity to antigens in DTPa-IPV/Hib

Schedule: 3, 4, and 5 months of age

Study Design:

Randomized (1:1), multicenter, open-label study.
231 healthy 3 mo old infants (57 days to 112 days of age) enrolled.
Blood samples obtained pre dose 1, and one month post dose 3

Statistical Analyses:

GMCs by ANCOVA, using pre-dose 1 GMCs as covariate.
Proportion responders by Fisher's exact.

Wyeth-Lederle Post-Marketing Study: Comparison of seroconversion/vaccine response rates to antigens in SBB's DTPa-IPV/Hib in infants with and without concurrent 7VPnC – Post dose 3, ATP cohort

Antigen	% Achieving Antibody Level			Difference in Proportion
	7VPnC Group* N=83	Control Group† N=75	P-Value‡	7VPnC Group – Control (95% CI)
PRP				
≥ 0.15 mg/mL	98.7	95.5	0.4975	3.2 (-6.2 - 17.9)
≥ 1.0 mg/mL	65.8	67.2	0.4937	-1.4 (-19.1 - 15.0)
Diphtheria				
≥ 0.01 IU /mL	100	100	0.5973	0.0 (-7.3 – 10.9)
≥ 0. 1 IU /mL	98.7	97.0		1.7 (-7.3 – 16.5)
Tetanus				
≥ 0.01 IU /mL	100	100		0.0 (-7.5 – 10.9)
≥ 0. 1 IU /mL	100	100		0.0 (-7.5 – 10.9)
PT				
≥ 2 fold rise	94.0	96.0	0.7223	-2.0 (-16.7 – 8.5)
≥ 4 fold rise	84.3	92.0	0.1516	-7.7 (-23.5 – 5.2)
Pertactin				
≥ 2 fold rise	85.7	98.5	0.0090	-12.8 (-28.5 – -1.1)
≥ 4 fold rise	80.0	95.5	0.0084	-15.5 (-32.0 - -2.0)
FHA				
≥ 2 fold rise	79.5	89.3	0.1260	-9.8 (-26.0 – 3.9)
≥ 4 fold rise	68.7	77.3	0.2831	-8.7 (-25.3 – 6.7)
Polio ≥1:10				
Type 1	100	96.9	0.2228	3.1 (-5.7 – 17.4)
Type 2	100	100	0.3769	0.0 (-7.9 – 11.2)
Type 3	100	100	0.3769	0.0 (-7.9 – 11.2)

*DTPa-IPV/Hib + 7VPnC at 3, 4, 5 months of age
†DTPa-IPV/Hib (no concurrent 7vPnC) at 3, 4, 5 months of age
‡P-value by Fisher's Exact Test

Wyeth-Lederle Post-Marketing Study: Comparison of DTPa-IPV/Hib Antibody GMC's in infants with and without concurrent 7VPnC – Post dose 3, ATP cohort

Antigen	GMC* Post Dose 3 Antibody			Ratio of GMC of 7VPnC Group to Control (95% CI)
	7VPnC Group**	Control Group†	P-Value‡	
	N=83	N=75		
PRP	1.68	1.94	0.5007	0.863 (0.560 – 1.329)
Diphtheria	1.15	0.61	<0.0001	1.959 (1.528 – 2.511)
Tetanus	3.79	4.44	0.2865	0.876 (0.686 – 1.119)
PT	37.8	44.3	0.3691	0.901 (0.716 – 1.133)
Pertactin	**138.5**	**236.3**	**0.0057**	**0.653 (0.483 – 0.881)**
FHA	60.6	67.5	0. 9664	0.995 (0.780 – 1.269)
Polio type 1	241	289	0.2306	0.763 (0.489 – 1.190)
Polio type 2	234	282	0.4381	0.847 (0.554 – 1.294)
Polio type 3	558	682	0.3370	0.878 (0.671 – 1.148)

*GMCs expressed as mcg/mL for Hib (PRP), IU/mL for diphtheria and tetanus, EU/mL for pertussis antigens, and as neutralizing antibody per mL for polio antigens.
**DTPa-IPV/Hib + 7VPnC at 3, 4, 5 months
†DTPa-IPV/Hib (no concurrent 7vPnC) at 3, 4, 5 months
‡P-value assesses the difference between treatment groups post-dose 3 using ANCOVA

Wyeth-Lederle Post-Marketing Study 118-503: Fever and antipyretic use within 3 days of SBB's DTPa-IPV/Hib with and without concurrent 7VPnC**

Systemic Reaction N=	Dose 1 (3 month)					Dose 2 (4 month)					Dose 3 (5 month)				
	7VPnC		Control Group		P-value*	7VPnC		Control Group		P-value*	7VPnC		Control Group		P-value*
	116	%	110	%		112	%	107	%		110	%	107	%	
Fever															
> 38°C	49	44.5	32	29.9	0.035	35	33.0	29	28.2	0.447	31	29.0	24	23.1	0.350
> 39.1C	4	3.8	5	4.8	0.747	3	2.9	2	1.0	0.683	5	4.7	1	1.0	0.212
Antipyretic use	**18**	**15.9**	**4**	**3.7**	**0.003**	11	9.8	5	4.7	0.195	8	7.3	4	3.8	0.374

*P-value assesses the difference between treatment groups and is calculated using Fisher's exact test.
**Analysis included all subjects who received at least one dose.

Reviewer comment: Data from a Wyeth-Lederle-sponsored German study of Prevnar given concurrently with SBB's DTPa-IPV/Hib (containing the same DTPa and IPV as DTPa-HepB-IPV) suggest that concurrent administration of these vaccines may interfere with the immune response to acellular pertactin. This study also demonstrated a trend towards increased fever (≥ 38°C) as well as a statistically significant increase in antipyretic use in those infants receiving DTPa-IPV/Hib concurrently with Prevnar. It is important to note that this study was not designed as a non-inferiority trial and had a small sample size. These data are shown to illustrate that data from studies of concurrent immunization of Prevnar with two DTPa products have shown diminution of the immune response to pertactin. The sample sizes are too small to draw definitive conclusions but these studies suggest the possibility of

immune interference with respect to pertactin when Prevnar is administered concomitantly with these DTPa vaccines.

Appendix 2: 4th Dose DTPa (Infanrix®) following a Primary Series of DTPa-HepB-IPV

While not formally considered a part of this BLA, SBB submitted summary safety and immunogenicity data on 4th (toddler) dose of Infanrix® or Infanrix®-based combinations following a primary series with DTPa-HepB-IPV. Only one of these studies (DTPa-HepB-IPV-015B) compared the safety and immunogenicity of a booster dose of Infanrix® and Hib vaccine in children receiving a primary series of DTPa-HepB-IPV versus separate injections of DTPa + Hep B + OPV.

Study	**Country**	**Infanrix® following primary series with DTPa-HepB-IPV**	
		N for safety evaluation	**N for immunogenicity evaluation**
DTPa-HepB-IPV/015B*	USA	125	116
DTPa-HepB-IPV-028	Germany	166	0
DTPa-HepB-IPV-061**	USA	94	90
Total		**385**	**206**

*DTPa-HepB-IPV-015B was the booster phase of Study DTPa-HepB-IPV-015.
***DTPa-HepB-IPV-016 was the booster phase of Study DTPa-HepB-IPV-044.

Study Synopsis: DTPa-HepB-IPV-015B

Title: An open study of the safety and immunogenicity of DTPa-HepB-IPV vaccine administered as a three dose primary series or in a sequential IPV/OPV schedule at 2, 4, and 6 months of age

Principle investigator: Dr. Joel Ward

Study period: 9/97 to 3/98

Objectives: To evaluate the safety and immunogenicity of Infanrix® (DTPa vaccine) administered simultaneously at separate sites with OmniHIB (Hib vaccine) as a booster in subjects 12 to 18 months of age who were primed with the following vaccines:
Group 1: DTPa-HepB-IPV + Hib at 2, 4, and 6 months
Group 2: DTPa-HepB-IPV + Hib administered at 2, and 4 months of age and DTPa-HepB + OPV + Hib administered at 6 months of age
Group 3: DTPa-HepB + IPOL® (IPV) + Hib administered at 2, 4, and 6 months of age
Group 4: DTPa (Infanrix®) + hepatitis B (Engerix-B) + OPV + Hib at 2, 4, 6 months of age

Study Design: open, single center, phase III. Blood samples were taken prior to and one month after booster dose

Number of subjects in booster study:

Enrolled: 232
Completed: 227
ATP cohort for immunogenicity: 210
ITT/ATP cohort for safety: 232

Appendix 2: 4th Dose DTPA (Infanrix®) Following a Primary Series of DTPa-HepB-IPV (Continued)

DTPa-HepB-IPV-015B: Seroprotection/ vaccine response and GMTs following booster dose of Infanrix® an Hib vaccine

Antibodies	Group 1 N=62		Group 2 N=54		Group 3 N=46		Group 4 N=48	
	%	GMT	%	GMT	%	GMT	%	GMT
Diphtheria	100	2.429	100	2.090	100	2.004	100	1.853
Tetanus	100	7.436	100	6.879	100	6.142	100	6.240
PT	100	148.5	100	146.8	100	100.0	100	110.0
FHA	98.0	251.0	100	289.5	96.8	279.5	100	367.6
PRN	98.4	351.7	100	328.8	95.3	302.6	93.5	355.0
PRP (≥1.0mcg/mL)	100	23.826	100	25.508	100	26.937	100	26.494

Primary vaccination :
Group 1: DTPa-HepB-IPV + Hib at 2, 4, and 6 months
Group 2: DTPa-HepB-IPV + Hib at 2, and 4 months and DTPa-HepB + OPV + Hib at 6 months
Group 3: DTPa-HepB + *IPV + Hib administered at 2, 4, and 6 months of age
Group 4: DTPa + hepatitis B + OPV + Hib at 2, 4, 6 months of age
Booster: All groups received DTPa + Hib
Seroprotection/vaccine response and GMT units as described in previous studies

DTPa-HepB-IPV-015B: Incidence of local and general symptoms following booster dose of Infanrix® and Hib vaccine

Symptom	Group 1			Group 2			Group 3			Group 4		
	%	95%CI		%	95%CI		%	95%CI		%	95%CI	
Redness												
Any	28.4	18.0	40.7	35.1	22.9	48.9	24.0	13.1	38.2	30.9	19.1	44.8
Grade 3	1.5	0.0	8.0	3.5	0.4	12.1	8.0	2.2	19.2	3.6	0.4	12.5
Pain												
Any	22.4	13.1	34.2	31.6	19.9	45.2	32.0	19.5	46.7	34.5	22.2	48.6
Grade 3	3.0	0.4	10.4	0.0	0.0	6.3	0.0	0.0	7.1	1.8	0.0	9.7
Swelling												
Any	13.4	6.3	24.0	15.8	7.5	27.9	18.0	8.6	31.4	23.6	13.2	37.0
Grade 3	0.0	0.0	5.4	1.8	0.0	9.4	2.0	0.1	10.6	3.6	0.4	12.5
Fever												
≥38°C	11.9	5.3	22.2	22.8	12.7	35.8	20.0	10.0	33.7	18.2	9.1	30.9
≥39.5°C	1.5	0.0	8.0	3.5	0.4	12.1	2.0	0.1	10.6	0.0	0.0	6.5

Primary vaccination :
Group 1: DTPa-HepB-IPV + Hib at 2, 4, and 6 months
Group 2: DTPa-HepB-IPV + Hib at 2, and 4 months and DTPa-HepB + OPV + Hib at 6 months
Group 3: DTPa-HepB + IPV + Hib administered at 2, 4, and 6 months of age
Group 4: DTPa + hepatitis B + OPV + Hib at 2, 4, 6 months of age
Booster: All groups received DTPa + Hib

Reviewer comment: In this small study, the safety and immunogenicity of Infanrix® (DTPa) toddler booster following a primary series of DTPa-HepB-IPV was comparable to the safety and immunogenicity following a primary series of separately administered DTPa, hepatitis B and oral polio vaccine.

FDA 3/7/01