BOX FILE

TGA

APPLICATION NO: 2005/2446

TITLE: INFANRIX - GLAXOSMITHKLINE AUSTRALIA PTY LTD

EARLIEST ACTION:	21/10/2005
LAST ACTION:	21/10/2005
AFDA/RDA CLASS:	62397
DISPOSAL ACTION:	D120
DESTROY YEAR:	2126

GlaxoSmithKline

CONFIDENTIAL

Category 1 Application

Changes to Product Information - Large swelling reactions

INFANRIX®
INFANRIX®-HIB
INFANRIX®-IPV
INFANRIX®-PENTA
INFANRIX®-HEXA

Module 2 – Common Technical Document Summaries

VOLUME 1 of 1

Refer Company Letter of: 21.10.2005
Application No: 2005/2446/2

Copy 4 of 4

October 2005

GlaxoSmithKline

Category 1 Application
Changes to Product information – Large swelling reactions
INFANRIX®, INFANRIX®-HIB, INFANRIX®-IPV, INFANRIX®-PENTA, INFANRIX®-HEXA

Module 2
Volume 1 of 1
Copy 4 of 4
October 2005

Document 1

CATEGORY 1 APPLICATION

Changes to Product Information - Large swelling reactions

INFANRIX®
INFANRIX®-HIB
INFANRIX®-IPV
INFANRIX®-PENTA
INFANRIX®-HEXA

Module 2 – Common Technical Document Summaries

VOLUME 1 of 1

Copy 4 of 4

All and any information contained in this document is to be regarded as commercial in confidence as it is a trade secret containing unpublished details and results of private research proprietary to GlaxoSmithKline Australia Pty Ltd, the disclosure of which to unauthorised persons (including its competitors) other than in accordance with Section 61 of the Therapeutic Goods Act 1989 (as amended) is prohibited without the express authority of GlaxoSmithKline Australia Pty Ltd.

GlaxoSmithKline Australia Pty Ltd
1061 Mountain Highway
Boronia
Australia 3155

October 2005

Confidential

Category 1 Application for changes to the Product Information
Large swelling reactions
Infanrix®, Infanrix®-Hib, Infanrix®-IPV, Infanrix®-Penta and Infanrix®-hexa

Module 2 Common Technical Document Summaries

MODULE 2 VOLUME

2.1 COMMON TECHNICAL DOCUMENT TABLE OF CONTENTS (m 2-5) ..... N/A

2.2 INTRODUCTION ..... N/A

2.3 QUALITY OVERALL SUMMARY ..... N/A

2.4 NONCLINICAL OVERVIEW ..... N/A

2.5 CLINICAL OVERVIEW 1
- 2.5.1 Product Development Rationale 1
- 2.5.2 Overview of Biopharmaceutics ..... N/A
- 2.5.3 Overview of Clinical Pharmacology ..... N/A
- 2.5.4 Overview of Efficacy ..... N/A
- 2.5.5 Overview of Safety 1
- 2.5.6 Benefits and Risks Conclusions 1
- 2.5.7 Literature References 1

2.6 NONCLINICAL SUMMARY ..... N/A

2.7 CLINICAL SUMMARY 1
- 2.7.1 Summary of Biopharmaceutics and Associated Analytical Methods ..... N/A
- 2.7.2 Summary of Clinical Pharmacology Studies ..... N/A
- 2.7.3 Summary of Clinical Efficacy ..... N/A
- 2.7.4 Summary of Clinical Safety 1
- 2.7.5 Literature References ..... N/A
- 2.7.6 Synopses of Individual Studies 1

Module 3 Quality

MODULE 3 VOLUME

3.1 MODULE 3 TABLE OF CONTENTS ..... N/A

3.2 BODY OF DATA ..... N/A

3.3 LITERATURE REFERENCES ..... N/A

Module 4 Non-clinical study reports

MODULE 4
VOLUME

4.1 MODULE 4 TABLE OF CONTENTS ..... N/A

4.2 STUDY REPORTS ..... N/A

4.3 LITERATURE REFERENCES ..... N/A

Module 5 : Clinical Study Reports

The current application for changes to the Product Information to include information on large swelling reactions after booster doses of DTPa-combination vaccines is being submitted for all GSK Infanrix-line vaccines. To facilitate review, one combined dossier is hereby submitted, as the supporting data are identical.

5.1 TABLE OF CONTENTS

MODULE 5
VOLUME

5.1 TABLE OF CONTENTS FOR CLINICAL STUDY REPORTS 1

5.2 TABULAR LISTING OF ALL CLINICAL STUDIES 1

5.3 CLINICAL STUDY REPORTS 1
- 5.3.1 Reports of Biopharmaceutic Studies ..... N/A
- 5.3.2 Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials ..... N/A
- 5.3.3 Reports of Human Pharmacokinetic (PK) Studies ..... N/A
- 5.3.4 Reports of Human Pharmacodynamic (PD) Studies ..... N/A
- 5.3.5 Reports of Efficacy and Safety Studies 1

In order to facilitate review of the clinical documentation, the paper (hard) copy of the dossier contains only the body of the study reports provided in this section. The complete reports, with appendices, are provided on CD ROM. Paper copies of the appendices can be supplied by the Applicant upon request.

5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication 1

208108/076 (HIB-076): Open, phase III clinical trial to assess the immunogenicity and reactogenicity of SB Biologicals' DTPa vaccine co-administered with one dose of unconjugated Hib vaccine in separate injections or mixed in the same syringe with SB Biologicals' Hib conjugate vaccine to healthy children, 12 to 18 months old, previously vaccinated at the age of 2, 4 and 6 months in study DTPa-HBV-IPV-036 (217744/036).
Principal investigator: [redacted]
Report date: Jul 10, 2000 (amended September 14, 2000) 1

208355/118 (APV-118): Randomised, blinded clinical study to assess the immunogenicity and reactogenicity of SB Biologicals' dTpa and DTPa vaccines and a commercial Td vaccine administered as a booster dose to healthy children 4 to 6 years

old, previously vaccinated with four doses of SB Biologicals' DTPa vaccine in the first two years of life.
Principal investigator: [redacted]
Report date: October 15, 1998 1

208355/120 (APV-120): Clinical study of the reactogenicity and immunogenicity of SB Biologicals' DTPa vaccine administered as a booster dose to healthy children 4 to 6 years of age, previously vaccination with four doses of SB Biologicals' DTPa vaccine in the first two years of life.
Principal investigator: [redacted]
Report date: February 2, 1999 1

213503/043 (DTPa-IPV-043): Double-blind clinical study to assess the immunogenicity and reactogenicity of a booster dose of GlaxoSmithKline Biologicals' Hib vaccine, conjugated with one of two tetnus toxoid carriers administered mixed as single injection with GSK Biologicals' DTPa-IPV vaccine at 17 to 19 months of age in infants primed in the study DTPa-IPV-039.
Principal investigators: [redacted] and [redacted]
Report date: January 28, 2002 1

213503/045 (DTPa-IPV-045): Open, randomized, phase IIIb, multi-site, clinical study to compare the immunogenicity and reactogenicity of GSK Biologicals' DTPa-IPV vaccine, with GSK Biologicals' DTPa (Infanrix™) and Aventis MSD's IPV vaccine (Imovax Polio®) administered separately to healthy children 4 to 6 years of age, previously vaccinated with three doses of DTPa and IPV or OPV vaccines during the first year of life in a 3, 5 and 11 to 12 month schedule.
Principal investigators: [redacted]
Report date: December 18, 2002 1

213503/046 (DTPa-IPV-046): Open, randomised phase IIIb, clinical trial to compare the immunogenicity and reactogenicity of GSK Biologicals' DTaP-IPV vaccine (INFANRIX®-IPV), with GSK Biologicals' DTaP (INFANRIX®) and Aventis Pasteur MSD's IPV vaccine (IPOL®) administered separately to healthy children 4 to 6 years of age, previously vaccinated with 4 doses of DTaP and polio vaccine, and co-administered with GSK Biologicals' MMR vaccine (PRIORIX™).
Principal investigators: [redacted]
Report date: March 5, 2004 (amended September 1, 2004) 1

213503/049 (DTPa-IPV-049): An open, multicentre, phase IV booster vaccination study to assess the immunogenicity and reactogenicity of GSK Biologicals' combined Infanrix™-IPV+Hib (DTPa-IPV/Hib) vaccine in healthy children aged 17 to 20 months who completed a three-dose primary vaccination course in study 217744/076 (DTPa-HBV-IPV-076).
Principal investigators: [redacted]
Report date: March 23, 2005 1

217744/058 (DTPa-HBV-IPV-058): Open, randomised, multicentre Phase III clinical trial to assess and to compare the reactogenicity of a booster dose of SB Biologicals' DTPa-HBV-IPV and Hib conjugate vaccines when mixed extemporaneously and

administered in a single injection and of SB Biologicals' DTPa-IPV/Hib with or without *Engerix-B™* vaccines administered in separate injections in 12 to 18 months old healthy children, previously vaccinated at the age of 3, 4 and 5 months in primary vaccination study DTPa-HBV-IPV-039 (217744/039).
Principal investigator: [redacted]
Report date: July 10, 2000 1

217744/059 (DTPa-HBV-IPV-059): Open, multicentre Phase III clinical trial to assess the immunogenicity and reactogenicity of SB Biologicals' DTPa-HBV-IPV and Hib conjugate vaccines when mixed extemporaneously and administered in a single injection as a booster dose to 12 to 18 months old healthy children, previously vaccinated at the age of 3, 4 and 5 months in primary vaccination study DTPa-HBV-IPV-048 (217744/048), with either three doses of the same vaccines or with three doses of DTPa-IPV/Hib and *Engerix-B™* vaccines administered in separate injections.
Principal investigator: [redacted]
Report date: July 3, 2000 1

217744/061 (DTPa-HBV-IPV-061): A Phase II, single-blinded randomized comparative study of the safety and Immunogenicity of a booster dose of SmithKline Beecham Biologicals' DTPa-HepB-IPV vaccine compared with Infanrix® when both vaccines are co-administered with OmniHIB® between 15 and 18 months of age following primary immunization at the age of 2, 4 and 6 months in the study DTPa-HepB-IPV-044 (CPMS N° 217744/044).
Principal investigators: s22 [redacted] s22 [redacted]
Report date: January 12, 2001 1

217744/062 (DTPa-HBV-IPV-062): Open, multicentre, phase III clinical study to assess the immunogenicity and reactogenicity of SB Biologicals' DTPa-HBV-IPV and Hib conjugate vaccines when mixed extemporaneously and administered in a single injection as a booster dose to 12 to 15 months old healthy children, previously vaccinated at the age of 6, 10 and 14 weeks in primary vaccination study DTPa-HBV-IPV-040 (217744/040), with three doses of the same vaccines either or not following a single dose of SB Biologicals' HBV vaccine (Engerix™-B) at birth.
Principal investigators: s2 [redacted] 2 [redacted]
Report date: August 22, 2000 2

217744/065 (DTPa-HBV-IPV-065): Open, randomized, multicentre, phase III clinical trial to assess the reactogenicity and immunogenicity of a booster dose of GlaxoSmithKline (GSK) Biologicals' DTPa-HBV-IPV/Hib vaccine, co-administered during the same visit with GSK Biologicals' MMR or Varicella vaccine, in children in their second year of life, previously vaccinated in the DTPa-HBV-IPV-039, -041, -043 or –057 primary vaccination studies.
Principal investigators: [redacted]
Report date: August 27, 2004 2

217744/066 (DTPa-HBV-IPV-066): Open, randomized, multicentre, phase III clinical trial to assess the reactogenicity and immunogericity of a booster dose of GlaxoSmithKline (GSK) Biologicals' DTPa-HBV-IPV/Hib vaccine, co-administered during

the same visit with GSK Biologicals' HAV vaccine (*Havrix™*), in children in their second year of life, previously vaccinated in the DTPa-HBV-IPV-039, -041, -043 or --057 primary vaccination studies (CPMS N) 217744/039, 041, 043 or 057).
Principal investigators: [redacted]
Report date: November 28, 2005 2

217744/074 (DTPa-HBV-IPV-074): Open, randomized, multicenter, phase IIIb clinical trial to assess the incidence of high grade fever (≥ 40.0 °C) within 4 days following a booster dose in the second year of life of GlaxoSmithKline (GSK) Biologicals' combined DTPa-HBV-IPV/Hib vaccine (*Infanrix HeXa™*) as compared to GSK Biologicals' combined DTPa-IPV/Hib (*Infanrix™* IPV+Hib) and HBV (*Engerix-B™* Kinder) vaccines administered concomitantly in separate injections to children previously primed with licensed vaccines according to the vaccination recommendations currently in place in Germany.
Principal investigator: [redacted]
Report date: June 11, 2002 2

217744/095 (DTPa-HBV-IPV-095): Open, multicentric, phase IV clinical trial to assess the immunogenicity and reactogenicity of GSK Biologicals' DTPa-HBV-IPV/Hib vaccine (Infanrix™ hexa) when given as a booster dose to children aged 11 to 23 months previously primed at 2, 4 and 6 months of age either with Aventis Pasteur's DTPa-HBV-IPV-Hib vaccine (Hexavac™) or GSK Biologicals' DTPa-HBV-IPV/Hib vaccine (Infanrix™ hexa) in study DTPa-HBV-IPV-086.
Principal investigator: [redacted]
Report date: March 10, 2005 2

404286/006 (Hepta-006): A Phase II, open randomized, controlled study to assess the immune memory induced by a primary vaccination course of GlaxoSmithKline Biologicals' (GSK Biologicals') DTPa-HBV-IPV extemporaneously mixed with GSK Biologicals' Hib-MenC by giving meningococcal AC polysaccharide, and the safety, reactogenicity and immunogenicity of a booster dose of GSK Biologicals' DTPa-HBV-IPV extempoaneously mixed with Hib-MenC to toddlers primed in study 404286/001.
Principal investigator: s22 [redacted]
Report date: October 22, 2003 2

455697/001 (DTPa-HAV-IPV-001): Open,randomised, multicentric Phase II clinical trial to assess the immunogenicity and reactogenicity of GSK Biologicals' DTPa-HAV-IPV and Hib-MenC vaccines when mixed extemporaneously and administered as a single booster dose to healthy children, 17 to 20 months of age, previously vaccinated with three doses of GSK Biologicals' DTPa-IPV/Hib vaccines in the DTPa-IPV-039 primary vaccination study.
Principal investigators: s22 [redacted]
Report date: July 23, 2002 2

711202/008 (MenC-TT-008): A phase II, open, controleed study to evaluate the persistence and the immune memory indicued by a primary vaccination course with GlaxoSmithKline (GSK) Biologicals' meningococcal serogroup C conjugate vaccine (one formulation) and GSK Biologicals' Haemophilus influenzae type b-meningococcal serogroup C conjugate vaccine (two formulations)

or Meningitec™ in healthy toddlers aged 12-15 months primed in study 711202/001.
Principal investigator: [redacted]
Report date: August 2004 2

5.3.5.2 Study Reports of Uncontrolled Clinical Studies ..... N/A
5.3.5.3 Reports of Analyses of Data from More Than One Study, Including Any Formal Integrated Analyses, Meta-analyses, and Bridging Analyses ..... N/A
5.3.5.4 Other Clinical Study Reports ..... N/A

5.3.6 Reports of Postmarketing Experience 2

5.3.7 Case Report Forms and Individual Patient Listings, When Submitted

Specific CRF pages used to record information on extensive local reactions. 2

5.4 LITERATURE REFERENCES 2

CONFIDENTIAL

Module 2.5 : Clinical Overview

TABLE OF CONTENTS

PAGE

2.5.1 PRODUCT DEVELOPMENT RATIONALE 3

2.5.2 OVERVIEW OF BIOPHARMACEUTICS 5

2.5.3 OVERVIEW OF CLINICAL PHARMACOLOGY 5

2.5.4 OVERVIEW OF EFFICACY 5

2.5.5 OVERVIEW OF SAFETY 5

2.5.5.1 Assessment of large swelling reactions following booster administration of GSK DTPa vaccines in clinical trials conducted by GSK 5

2.5.5.1.1 Overview of study design and conduct 8

2.5.5.1.2 Overview of methodology, as it pertains to collection of data on large swelling reactions 8

2.5.5.1.3 Overview of data obtained for children immunised during the second year of life with a fourth dose of DTPa or DTPa-containing vaccine 9

2.5.5.1.4 Overview of data obtained for children immunised at 4-6 years of age with a fourth or fifth dose of DTPa or DTPa-containing vaccine 14

2.5.5.2 Assessment of large swelling reactions following booster administration of GSK DTPa vaccines in clinical trials not conducted by GSK 18

2.5.5.2.1 Multicenter Acellular Pertussis Trial (MAPT) 18

2.5.5.2.2 Fifth dose study conducted by Scheifele and co-workers 19

2.5.5.3 Assessment of large swelling reactions following administration of GSK DTPa vaccines during post-marketing surveillance 19

2.5.6 BENEFITS AND RISKS CONCLUSIONS 20

2.5.7 LITERATURE REFERENCES 23

LIST OF ABBREVIATIONS

ATP	According to protocol
CI	confidence interval
CRF	Case Report Form
DTPa	Diphtheria-tetanus-acellular pertussis
DTPa/Hib	Diphtheria-tetanus-acellular pertussis/*Haemophilus influenzae* type b
DTPa-HepB	Diphtheria-tetanus-acellular pertussis-hepatitis B
DTPa-IPV	Diphtheria-tetanus-acellular pertussis-inactivated polio
DTPa-IPV/Hib	Diphtheria-tetanus-acellular pertussis-inactivated polio/ *Haemophilus influenzae* type b
DTPa-HBV-IPV	Diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated polio
DTPa-HBV-IPV/Hib	Diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated polio/*Haemophilus influenzae* type
DTPw	Combined diphtheria/tetanus/whole cell pertussis vaccine
GSK	GlaxoSmithKline
Hib	*Haemophilus influenzae* type b
IPV	Inactivated poliomyelitis vaccine
MAPT	Multicenter Acellular Pertussis Trial
PSUR	Periodic Safety Update Report
SPC	Summary pf Product Characteristics

2.5.1 PRODUCT DEVELOPMENT RATIONALE

Whole-cell pertussis vaccines, prepared from inactivated *B. pertussis* organisms, were first introduced in the 1950s. They were highly efficacious against disease and their wide-spread use caused the incidence of whooping cough to rapidly fall. Despite this, the use of these vaccines remained problematic due to the fact that they induced fever and injection site reactions in a high percentage of recipients. In addition, the rare occurrence of more severe reactions, in conjunction with anecdotal reports of neurological complications, led to the search for less reactogenic vaccines against pertussis. This second generation of pertussis vaccines, acellular pertussis vaccines, were formulated to contain a limited number of well defined and highly purified *B. pertussis* antigens, selected on the basis of their contribution to the pathogenicity of *B. pertussis* in *in vitro* and *in vivo* models.

Six different combined diphtheria-tetanus-acellular pertussis (DTPa) vaccines were initially licensed in Japan in 1981. Licensure was based on the demonstration of diminished local and systemic reactogenicity, and equal or superior immunogenicity, with respect to whole-cell vaccines. Following licensure, routine vaccination was initiated in children from two years of age.

The success of vaccination with acellular pertussis vaccines in Japan stimulated efforts to develop other, similar vaccines to replace whole-cell vaccines in Western schedules, i.e. primary vaccination during the first year of life, followed by one or more booster doses. Several candidate vaccines were evaluated in clinical trials and subsequently licensed, first for booster use then for primary immunisation, once efficacy had been established. One of the first vaccines licensed was GlaxoSmithKline Biologicals' DTPa vaccine, *Infanrix*.

Early trials showed a marked decrease in reactogenicity for DTPa vaccines with respect to DTPw when they were used as booster doses following priming with DTPw. In 1995, the first data from longitudinal studies of children who had been both primed and boosted with DTPa became available. These trials indicated that the incidence of local reactions increased significantly upon boosting, although they remained below the level seen after a fourth or fifth dose of DTPw (Halperin et al., 1995; Halperin et al., 1996; Halperin et el, 1999; Pichichero et al, 1997; Schmitt et al, 1996; Schmitt et al, 1997a). The most unexpected event after boosting was the occurrence of particular large local redness and/or swelling reactions, reported as involving the whole injected thigh. In fact, swelling reactions "with swelling of the arm down to the elbow or the wrist" had been previously described in Japanese children administered DTPa vaccines but had been considered as "extremely rare" (Noble et al, 1987).

These large swelling reactions have been shown to begin generally within 48 hours of vaccination and to resolve spontaneously without sequelae. Data from the Multicenter Acellular Pertussis Trial (MAPT), sponsored by the US National Institute of Allergy and Infectious Diseases (NIAID), showed that swelling of the entire thigh occurred with the DTPa vaccines from different manufacturers administered as a fourth dose in the second year of life (Rennels et al, 2000). The number of subjects administered a fifth dose in this trial was limited and large swelling reactions were not observed in any vaccince;

however, entire upper arm swelling has been reported after a fifth dose of DTPa in other trials (Liese et al, 2001).

Comparison of data across these and other published trials is made difficult by the lack of a standard definition and terminology. In published reports, the terms "extensive" or "large" have been used to describe reactions which are greater than a certain diameter (usually ≥ 5 cm), in addition to reactions which lead to a noticable increase in limb circumference and/or extend to adjacent joints. In some trials, redness, rather than swelling, has been the parameter evaluated. Post-marketing reports describe "swelling or oedema of the entire limb" (Summary of Product Characteristics for Hexavac™, Sanofi-Pasteur) or "circumferential limb swelling" (Summary of Product Characteristics for Pediacel™, Sanofi-Pasteur-MSD).

In the light of these data, it is now evident that there are two different kinds of large local reactions - those which involve a delimited area around the injection site and those which extend diffusely over the entire injected limb. In order to more accurately document large swelling reactions following administration of GSK DTPa and DTPa-containing vaccines, the Company put procedures in place to gather information in the clinical trial setting.

Reports received through routine post-marketing surveillance have, in addition, been analysed.

Due to the frequency of large swelling reactions, and their potential as a source of concern for the parents of the vaccinees, the Company wishes to amend the SPCs of all *Infanrix*-line products to include information on these reactions.

To do this, information from all *Infanrix*-line vaccines has been collated in a unique variation dossier. This is justified by the fact that similar observations/conclusions can be made for all *Infanrix*-line products, as will be shown in later sections of the current document.

The Company intended to submit this variation first for *Infanrix*-line vaccines registered by the Centralised Procedure, then for vaccines registered by Mutual Recognition and/or nationally with the intention of harmonising, as much as possible, the Prescribing Information across *Infanrix*-line products. The dossier was submitted to the CHMP for *Infanrix penta* and *Infanrix hexa* in April 2005, with the CHMP Opinions given in July 2005. The wording agreed by the CHMP concerning swelling reactions for *Infanrix penta* and *Infanrix hexa* is hereby proposed as an amendment to the Prescribing Information for *Infanrix*. In addition, during the variation procedure, the Company agreed to add a statement concerning an increase in the incidence of reactions when vaccines were administered as a booster to children 4-6 years of age; as *Infanrix* may be used as a booster in this age group in some countries, this statement will be added whenever appropriate.

2.5.2 OVERVIEW OF BIOPHARMACEUTICS

Not Applicable

2.5.3 OVERVIEW OF CLINICAL PHARMACOLOGY

Not Applicable

2.5.4 OVERVIEW OF EFFICACY

Not Applicable

2.5.5 OVERVIEW OF SAFETY

2.5.5.1 Assessment of large swelling reactions following booster administration of GSK DTPa vaccines in clinical trials conducted by GSK

Clinical trial data has been obtained for all DTPa combinations which have been licensed for booster use in the EU. Table 1 provides a list of the abbreviations used for each of the vaccine formulations considered, and their indications. Most of the data in the clinical trial setting has been obtained for the DTPa-IPV/Hib and DTPa-HBV-IPV/Hib combinations, which are registered for use as boosters up to 2 years of age.

A general overview of the 18 completed clinical trials submitted in the present dossier is given in Table 2. All enrolled subjects had previously received 3 or 4 doses of a DTPa-containing vaccine for primary/booster immunisation. Information from a total of 13604 doses of GSK vaccines has been analysed.

Table 1. GSK DTPa combination vaccines and their abbreviations and indications

Abbreviation	Components	Usual trade name(s)	EU Registration procedure	Booster use
DTPa	Diphtheria-tetanus-acellular pertussis	Infanrix	National	up to adolescence
DTPa/Hib	Diphtheria-tetanus-acellular pertussis/*Haemophilus influenzae* type b	Infanrix+Hib	National	up to 2 years of age
DTPa-HepB	Diphtheria-tetanus-acellular pertussis-hepatitis B	Infanrix-HepB	Centralised Procedure	not licensed for booster use in the EU region – up to 2 years of age outside of EU
DTPa-IPV	Diphtheria-tetanus-acellular pertussis-inactivated polio	Infanrix-Polio Infanrix-IPV	Mutual Recognition	up to adolescence
DTPa-IPV/Hib	Diphtheria-tetanus-acellular pertussis-inactivated polio/ *Haemophilus influenzae* type b	Infanrix-Polio/Hib Infanrix-IPV+Hib	Mutual Recognition/ National	up to 2 years of age
DTPa-HBV-IPV	Diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated polio	Infanrix penta	Centralised Procedure	up to 2 years of age
DTPa-HBV-IPV/Hib	Diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated polio/*Haemophilus influenzae* type b	Infanrix hexa	Centralised Procedure	up to 2 years of age

Table 2. Overview of studies submitted in the current dossier

Study (country)	Vaccine and number of doses administered in each trial					
	DTPa	DTPa/Hib	DTPa-IPV	DTPa-IPV/Hib	DTPa-HBV-IPV	DTPa-HBV-IPV/Hib
4th dose 2nd year of life						
208108/076 (Australia)	70	219				
213503/043 (Lithuania)				200		
213503/049 (Spain)				344		
217744/058 (Germany)				456		693
217744/059 (Switzerland)						443
217744/061 (USA)	96				99	
217744/062 (The Philippines)						237
217744/065 (Germany)						175
217744/066 (Germany)						82
217744/074 (Germany)				4018		4032
217744/095 (Germany)						329
404286/006 (Germany)						191
455697/001 (Lithuania)				163		
711202/008 (Germany)						459
4th dose 4-6 years of age						
213503/045 (Italy, Sweden)	205		211			
5th dose 4-6 years of age						
208355/118 (Germany)	107					
208355/120 (Germany)	413					
213503/046 (Australia)	181		181			
Total doses	**1072**	**219**	**392**	**5181**	**99**	**6641**

2.5.5.1.1 Overview of study design and conduct

Only children free of obvious health problems were enrolled into the trials. Inclusion/exclusion criteria were clearly listed in the protocol and in the individual Case Report Forms (CRFs).

All GSK studies were conducted by experienced investigators and monitored by appropriately trained GSK Biologicals Clinical Research Associates. The design and conduct of each study took into account the Good Clinical Practice guidelines in use at the time of initiation of each study, and the Declaration of Helsinki and its amendments were respected. All study protocol underwent ethics review board appraisal. Written informed consent was obtained from the parents or guardians of subjects in all studies. A physical examination and recording of medical history established eligibility for enrolment in the studies. Documentation of each procedure was kept. Studies including multiple groups were randomised.

Children aged from 12-24 months received the vaccine in the anterolateral aspect of the thigh, with the exception of study 208108/076, where the vaccine was administered in the deltoid region. All children aged 4-6 years received the vaccine in the deltoid region. Vaccines were administered intramuscularly.

2.5.5.1.2 Overview of methodology, as it pertains to collection of data on large swelling reactions

In all trials, parents/guardians of vaccinated children were provided with diary cards for the recording of information on local and general symptoms after vaccination. This information was transcribed into individual CRFs for each child.

Studies 208355/118 and 208355/120 were the first to be initiated. In these trials, parents/guardians were instructed to contact the investigator immediately if their child manifested signs or symptoms that raised concern. Parents who contacted the investigator to report swelling reactions were requested to bring the child to the investigational site, where information on reactions deemed by the investigator to be "notable" was encoded onto specific pages in the CRF. This information included the dates of onset and resolution, intensity of the reaction (i.e. level of discomfort and/or interference with daily activities), the circumference (in millimeters) of the injected limb and the opposite limb, the presence and extent (confined to the injection site or more extensive involvement of the limb) of any associated redness, pain and/or warmth, as well as the body temperature.

In the subsequent 16 trials, the parents/guardians were specifically instructed to contact the investigator if they observed any large injection site swelling. With the exception of study 213503/045, this instruction was also repeated on the diary cards distributed to the parents/guardians after vaccine administration. Large injection site swelling was defined as swelling with a diameter > 50 mm, noticable diffuse swelling or noticable increase in circumference of the injected limb. The child was to be brought to the investigational site for examination.

Supplemental pages in the subject's CRF were provided in order to collect data on these cases. Information on the start date, end date and intensity of the swelling, the circumference (in millimeters) of the injected limb and the opposite limb, the presence and extent (confined to the injection site or more extensive involvement of the limb) of any associated redness, pain and/or warmth, as well as the body temperature, was requested. Space was also provided for the investigator to further describe the swelling reaction, should this be necessary. In addition, and as an aid to analysis of the swelling reactions at GSK, the investigator was requested to classify each reaction to three types, as follows:
– type 1: local swelling around the injection site, not involving adjacent joints
– type 2: diffuse swelling, not involving adjacent joints
– type 3: swelling involving adjacent joints.
The term "type" was used to avoid confusion with "grade", which was used to evaluate the intensity/severity of the other solicited symptoms.

The CRF pages used for recording information on large swelling reactions in each of the studies submitted are provided in Module 5.

Reaction types 2 and 3 correspond to different degrees of the same phenomenon, i.e. the large, diffuse swelling reactions described above. Due to the low number of type 3 reports, the data concerning type 2 and type 3 reactions have been pooled to permit meaningful comparison with data from type 1 reactions.

2.5.5.1.3 Overview of data obtained for children immunised during the second year of life with a fourth dose of DTPa or DTPa-containing vaccine

Data on the occurrence of large swelling reactions when DTPa or DTPa-containing combinations are used as a fourth dose in the second year of life have been obtained in 14 clinical trials (Table 2). Large swelling reactions were a solicited adverse event in all trials.

The overall frequency of reports of large swelling reactions, and the frequencies for each of the individual vaccines administered for the booster dose are shown in Table 3. (An analysis of the frequency of reports as a function of both primary and booster vaccines administered was not performed, due to the relatively low number of subjects in some of the cohorts which would make the analysis meaningless.)

As shown in the table, reactions of this type were reported for all of the DTPa-combination vaccines evaluated as boosters in the clinical trial setting.

The frequencies for DTPa-HBV-IPV/Hib (obtained by pooling the results from 9 studies; see Table 1) and DTPa-IPV/Hib (pooled results from 5 studies) are similar, and indeed, were similar in both studies 217744/058 and 2117744/074 where the two vaccines were directly compared; incidences of 3.5% (95% CI: 2.0-5.6) and 1.9% (95% CI: 1.0-3.2) were observed for DTPa-IPV/Hib and DTPa-HBV-IPV/Hib, respectively, in study

217744/058, the respective incidences were 1.8% (95% CI: 1.4-2.3) and 2.6% (95% CI: 2.1-3.1) in study 217744/074.

For DTPa-HBV-IPV/Hib, the across-trial variablility was low, with frequencies ranging from 1.2% (in studies 217744/066 and 217744/095) to 3.4% (in study 217744/059). For DTPa-IPV/Hib, the frequencies across the 5 trials ranged from 1.8% (in study 1774/074) to 8.0% (in study 455697/001).

Importantly, there seems to be no correlation between the incidence of large swelling reactions and the number of antigenic components in the vaccine. Of note, relatively higher frequencies of these reports were observed for DTPa and DTPa/Hib. This higher frequency is probably exclusively due to the fact that all of the data for DTPa/Hib, and half of the data for DTPa, come from one clinical trial, 208108/076. In this trial, vaccine was administered in the deltoid region which is known to induce in a higher frequency of local reactions with respect to injection in the anterolateral thigh (Scheifele et al, 1992; Schmitt et al, 1997b). Indeed, the results from study 217744/061 show that the frequency of large swelling reaction reports was not different for DTPa with respect to DTPa-HBV-IPV, being approximately 1% for both vaccines when they were administered in the thigh.

Table 3. Frequency of reports of large swelling reactions, overall and by vaccine, in trials where these reactions were solicited – trials evaluating DTPa-containing vaccines as a fourth dose during the second year of life

Booster Vaccine	N subjects	*n* reports	Frequency (%)
All	**12306**	**326**	**2.6 (2.4-2.9)**
DTPa-HBV-IPV/Hib	6641	157	2.4 (2.0-2.8)
DTPa-IPV/Hib	5181	137	2.6 (2.2-3.1)
DTPa-HBV-IPV	99	1	1.0 (0-5.5)
DTPa/Hib	219	18	8.2 (4.9-12.7)
DTPa	166	13	7.8 (4.2-13.0)

The analysis of all reports for type I and type2/3 reactions is provided in Table 4. Type I reactions, i.e. those limited to the injection site, were the most frequent type for each of the vaccines administered during the second year of life, representing approximately 75% of reports overall.

Table 4. Frequency of type 1 and type 2/3 swelling reactions, overall and by vaccine, in trials where these reactions were solicited – trials evaluating DTPa-containing vaccines as a fourth dose during the second year of life

	N subjects	N reports	Type 1 reaction reports		Type 2/3 reaction reports	
			n	%	n	%
All	**12306**	**326***	**236**	**1.9 (1.7-2.2)**	**79**	**0.6 (0.5-0.8)**
DTPa-HBV-IPV/Hib	6641	157*	115	1.7 (1.4-2.1)	41	0.6 (0.4-0.8)
DTPa-IPV/Hib	5181	137*	93	1.8 (1.5-2.2)	34	0.7 (0.5-0.9)
DTPa-HBV-IPV	99	1	0	-	1	1.0 (0-0.5)
DTPa/Hib	219	18	15	6.8 (3.9-11.0)	3	1.4 (0.3-4.0)
DTPa	166	13	13	7.8 (4.2-13.0)	0	-

* includes 11 reactions not typed by the investigator (1 reaction observed after DTPa-HBV-IPV/Hib, 10 reactions after DTPa-IPV/Hib)

The size of the swelling reactions and the signs associated with type 1 and type 2/3 reactions are shown in Table 5. (As in virtually all instances, the large swelling reactions were accompanied by redness, overall incidences of redness have not been tabulated.) Values for the total cohort (which includes subjects who had a large swelling reaction) have also been tabulated.

There was no trend towards a higher incidence of fever (temperature ≥ 38°C when measured rectally), or grade 3 fever (temperature > 39.5°C when measured rectally) with reaction type. Indeed, the incidences of these symptoms in the vaccinees who experierenced large swelling reactions were similar to those seen in the total cohort.

Although the results need to be interpreted with caution given the small number of subjects considered, it can be noted that grade 3 impairment (defined as reaction preventing normal everyday activities) and grade 3 pain (defined as the child crying when the limb was moved or the limb was spontaneously painful) tended to be more frequent in children who experienced type 2/3 reactions with respect to those who experienced type 1 reactions. Importantly, the overall incidences of these symptoms in children who experienced large swelling reactions remained low. Indeed, grade 3 pain was reported just as frequently in the group of children who experienced large swelling reactions in comparison to the total cohort.

An increase in limb circumference was seen for all types of large swelling reactions, but the mean difference between limb circumference for type2/3 swelling tended to be larger than for type 1 swelling.

Ninety-eight percent of all cases of large swelling had their onset within 48 hours of vaccination. All cases (with the exception of one, where the outcome was indicated as unknown) were reported as having resolved. The reported mean time to resolution was

3.4 days. Eighty-two percent of all cases resolved within 4 days; all but one case resolved within 15 days. The reported duration was 17 days for this child.

Table 5. Signs associated with large swelling reactions – trials evaluating DTPa-containing vaccines as a fourth dose during the second year of life

	N	Swelling		Swelling diameter [mean (sd†)]	Difference in limb circumference [mean (sd†)]	Grade 3 pain		Grade 3 impairment		Fever (≥ 38°C rectal)‡		Fever (> 39.5°C rectal)‡	
		n	%			n	%	n	%	n	%	n	%
Type 1	12306	236	1.9	74.4 (30.5)	16.3 (12.7)	10	4.2	4	1.7	57	24.3	10	4.2
Type 2/3	12306	79	0.6	90.7 (49.1)	28.1 (18.8)	6	7.6	4	5.1	23	29.1	4	5.1
Type not specified	12306	11	0.08	73.5 (26.5)	36.9 (22.8)	0	0.0	0	0.0	2	18.2	0	0.0
All subjects with large swelling reactions	12306	326	2.6 (2.4-2.9)*	-	-	16	4.9 (2.8-7.8)*	8	2.5 (1.1-4.9)*	92	28.2 (23.4-33.4)*	14	4.3 (2.4-7.1)*
Total cohort	4080**	1406	34.5 (33.0-35.9)*	-	-	166	4.1 (3.5-4.7)*	na	na	1455	35.7 (34.2-37.2)*	114	2.8 (2.3-3.3)*

* 95% CI

† standard deviation

** cohort does not include study 2117744/074 as only large swelling reactions were solicited in this trial

‡ note: some children received other vaccines concomitantly with DTPa vaccines – an influence of the co-administered products on the incidence of fever cannot be excluded

2.5.5.1.4 Overview of data obtained for children immunised at 4-6 years of age with a fourth or fifth dose of DTPa or DTPa-containing vaccine

Of the GSK DTPa combination vaccines, only DTPa and DTPa-IPV are licensed for use in pre-school aged children in Europe. Data are available from four trials in which children of 4-6 years of age received either DTPa or DTPa-IPV.

In two trials, large swelling reactions were specifically solicited. In study 213503/045, children had been previously primed with DTPa according to a 3,5, 11/12 month schedule; in study 213503/046, children had previously been administered 4 doses of DTPa vaccines at approximately 2, 4, 6 and 18 months of age. The results from these two trials are given in Tables 6 and 7 below.

Within each trial, the frequencies of large swelling reaction reports were similar for the two vaccines tested (Table 6). There were also no differences between the distributions of the types of reactions (Table 7). As observed for children in the second year of life, type 1 reactions were predominant, representing around three-fourths of all reactions reported in study 213503/045 and two-thirds of all reactions reported in study 213503/046.

Similarly to what was observed in children vaccinated during the second year of life, there was a slight trend towards a higher incidence of grade 3 pain in children who experienced type 2/3 reactions with respect to type 1 reactions, but the overall incidences of grade 3 symptoms including pain remained low and overall not different from incidences observed in the total cohort (Table 8).

Table 6. Frequency of reports of large swelling reactions, overall and by vaccine, in trials where these reactions were solicited – trials evaluating DTPa-containing vaccines as a fourth or fifth dose at 4-6 years of age

	Booster Vaccine	N subjects	n reports	Frequency (%)
4th dose	All	416	63	15.1 (11.8-19.0)
	DTPa-IPV	211	28	13.3 (9.0-18.6)
	DTPa	205	35	17.1 (12.2-22.9)
5th dose	All	362	92	25.4 (21.0-30.2)
	DTPa-IPV	181	43	23.8 (17.8-30.6)
	DTPa	181	49	27.1 (20.7-34.2)

Table 7. Frequency type 1 and type 2/3 swelling reactions, overall and by vaccine, in trials where these reactions were solicited – trials evaluating DTPa-containing vaccines as a fourth or fifth dose at 4-6 years of age

Vaccine dose		N subjects	N reports	Type 1 reaction reports		Type 2/3 reaction reports	
				n	%	n	%
4th dose	**All**	**416**	**63**	**48**	**11.5 (8.6-15.0)**	**15**	**3.6 (2.0-5.9)**
	DTPa-IPV	211	28	21	10.0 (6.3-14.8)	7	3.3 (1.3-6.7)
	DTPa	205	35	27	13.2 (8.9-18.6)	8	3.9 (1.7-7.5)
5th dose	**All**	**362**	**92**	**62**	**17.1 (13.4-21.4)**	**30**	**8.3 (5.7-11.6)**
	DTPa-IPV	181	43	32	17.7 (12.4-24.0)	11	6.1 (3.1-10.6)
	DTPa	181	49	30	16.6 (11.5-22.8)	19	10.5 (6.4-15.9)

Data for children 4-6 years of age are also available from two studies (208355/118 and 208355/120) where DTPa vaccine was administered as a fifth dose. In these studies, the parents were instructed to report "signs/symptoms that raised concern"; large swelling reactions were not specifically solicited.

During study 208355/118, the parents of 9 (8.4%) subjects of a total of 107 vaccinated with DTPa contacted the investigator to report swelling. Three (2.8%) cases of swelling were considered as "notable" by the investigator; two cases were described as extending from the elbow to the shoulder and one case was described as swelling extending to the chest. All three cases had their onset within 2 days of vaccination. All were accompanied by local redness, pain and warmth. Increases in limb circumference were observed but all were ≤ 7 cm. No fever was reported. All reactions resolved within 5 days. One of these subjects had also experienced a large swelling reaction after the fourth dose of DTPa vaccine in a GSK-sponsored clinical trial (APV-039B).

During study 208355/120, 26 (6.3%) subjects with swelling were seen by the investigator of a total of 413 children vaccinated with DTPa. Two (0.5%) cases were considered as "notable" by the investigator; both described as a swelling of the upper arm to the elbow. One reaction included the shoulder. Both occurred within 3 days of vaccination and were accompanied by local redness. Only one subject experienced pain and warmth. No fever or impairment of function was reported. Both cases resolved within 4 days.

Table 8. Signs associated with large swelling reactions – trials evaluating DTPa-containing vaccines as a fourth or fifth dose at 4-6 years of age

		N	Swelling n	Swelling %	Swelling diameter [mean (sd†)]	Difference in limb circumference [mean (sd†)]	Grade 3 pain n	Grade 3 pain %	Grade 3 Impairment n	Grade 3 Impairment %	Fever (≥ 37.5°C oral/axillary)‡ n	Fever (≥ 37.5°C oral/axillary)‡ %	Fever (> 39°C oral/axillary)‡ n	Fever (> 39°C oral/axillary)‡ %
4th dose	Type 1	416	48	11.5	92.7 (31.6)	18.7 (18.2)	0	0.0	1	2.1	4	8.3	0	0.0
	Type 2/3	416	15	3.6	140.5 (54.2)	26.0 (6.7)	1	6.7	0	0.0	3	20.0	0	0.0
	All subjects with large swelling reactions	416	63	15.1	-	-	1	1.6 (0-8.5)*	1	1.6 (0-8.5)*	7	11.1 (4.6-21.6)*	0	0.0
	Total cohort	416	218	52.4	-	-	15	3.6 (2.0-5.9)*	na	na	78	18.8 (15.1-22.8)*	4	1.0 (0.3-2.4)*
5th dose	Type 1	362	62	17.1	76.6 (28.5)	20.8 (16.2)	3	3.2	1	1.6	6	9.7	0	0.0
	Type 2/3	362	30	8.3	104.0 (42.2)	31.3 (15.8)	2	6.7	1	3.3	3	10.0	0	0.0
	All subjects with large swelling reactions	362	92	25.4	-	-	5	5.4 (1.8-12.2)*	2	2.2 (0.3-7.6)*	9	9.8 (4.6-17.8)*	0	0.0
	Total cohort	362	216	59.7	-	-	18	5.0 ((3.0-7.7)*	na	na	92	25.4 (21.0-30.2)*	4	1.1 (0.3-2.8)*

* 95% CI

† standard deviation

‡ note: some children received other vaccines concomitantly with DTPa vaccines – an influence of the co-administered products on the incidence of fever cannot be excluded

In the four studies in children 4-6 years of age, swelling reactions usually occurred within 48 hours of vaccination. The reported mean time to resolution was 4.0 days; 78% of all cases were reported as having resolved within 4 days, with all but two cases having resolved within 15 days (reported duration of 18 and 57 days, respectively). These data are overall similar to what was observed in children during their second year of life.

It is noteworthy that the frequency of reports is markedly lower in studies 208355/118 and 120 (6-8%) with respect to what was observed in study 213503/046 (25%). There are several possible reasons for this observation, the most likely are:

1. soliciting of large swelling reactions. In study 213503/046, instructions for the reporting of large swelling reactions were indicated on the diary cards distributed to the parents, in studies 208355/118 and 120 these instructions were not present. The positive effect of active soliciting on reaction reporting can be considerable. For example, drowsiness was a solicited symptom in study 213503/046, where it was reported for 24% of the vaccinees over the first four day period after vaccination. It was not solicited in study 208355/118; only 8 cases (2%) of fatigue/somnolence were reported after immunisation.

2. site of injection and vaccination technique. During the analysis of the data from study 213503/046, the Company was struck by the number of type 3 reports, specifically reports of swelling involving the shoulder. It became apparent that children in this trial were vaccinated closer to the shoulder in comparison with other 5th dose trials – a proportion of the type 3 cases effectively involved the shoulder but were not diffuse or oedematous. Of the 20 reports which involved the proximal shoulder joint, 10 were limited to the shoulder joint, with no further extension above or below the joint; 6 extended above the shoulder but with no further extension. Only four were diffuse, involving the whole upper arm (including both the shoulder and the elbow joints). Vaccination close to the shoulder may result in more frequent superficial injection of the vaccine. It is well known that deep subcutaneous injection of alum-adsorbed vaccines increases local reactogenicity with respect to intramuscular injection (Blennow and Gränstrom, 1989). Furthermore, failure to inject deep into the deltoid may explain why children with a high body mass index are 3-4 times more likely to develop large injection site redness when vaccinated with a fifth dose of DTPa (Scheifele et al, 2001; Jackson et al, 2002).

3. vaccination history. In the MAPT, children who received different vaccines tended to experience more swelling reactions after a fifth dose than children who had received 5 doses of the same vaccine, although the differences were not statistically significant (Rennels et al, 2000). All subjects enrolled in studies 208355/118 and 120 had received four doses of GSK's DTPa. In study 213503/046, vaccinees had received 4 doses of a DTPa vaccine from any manufacturer.

Other factors which may have played a less prominent role, but which are important in the understanding of the mechanisms underlying large swelling reactions, will be discussed in Module 2.5.6.

Albeit difficult to quantify from the results obtained, available data support the conclusion that there is an increase in the incidence of large swelling reactions between

the fourth dose given during the second year of life and the fifth dose given at 4-6 years of age. GSK-sponsored clinical trial data in children followed up for all 5 doses of the vaccination course are limited, with differences in methodology being additional confounding factors to analysis. This aside, the frequency of swelling reactions ≥ 50 mm after a fourth dose of DTPa in study APV-039B was 8.1% (95% CI: 6.9-9.4) and after a fifth dose in studies 208335/118 and 120 was 20.2% (95% CI: 16.6-24.1). A noticable increase in thigh circumference, which resulted in the child being seen by the investigator, was observed with a frequency of 1.1% in study APV-039B (Schmitt et al, 1997a); approximately 7% of the parents of children from the same cohort administered a fifth dose contacted the investigator in studies 208355/118 and 120.

Data for GSK's DTPa vaccine obtained in the MAPT will be discussed in the section which follows.

An increase in local reactogenicity from the fourth to the fifth dose has also been observed in another longitudinal cohort study which evaluated Biken DTPa vaccine; redness and swelling were reported as occurring after the fourth dose with respective incidences of 38.7% and 21.7%. They were reported after the fifth dose in approximately 60% of all vaccinated children, with redness or swelling > 5 cm observed for 31.0% and 25.0% of the cohort, respectively (Liese et al, 2001).

2.5.5.2 Assessment of large swelling reactions following booster administration of GSK DTPa vaccines in clinical trials not conducted by GSK

2.5.5.2.1 Multicenter Acellular Pertussis Trial (MAPT)

The MAPT, sponsored by the US National Institute of Allergy and Infectious Diseases (NIAID), compared the safety and immunogenicity of 13 DTPa vaccines and two DTPw vaccines in a total cohort of 2342 infants.

One hundred and twenty infants were enrolled to receive a three-dose primary course of GSK's tricomponent DTPa vaccine at 2, 4 and 6 months (Decker et al, 1995); 76 of these received a fourth dose of the same vaccine at 15-20 months of age (Pichichero et al, 1997) and 22 received a fifth dose at 4-6 years of age (Pichichero et al, 2000).

Information on local reactions was collected using diary cards. Large swelling reactions (defined as swelling with a diameter > 50 mm) were observed in 6.6% of the vaccinees after the 4th dose of GSK's DTPa and in 36.4% after the fifth dose.

After the study was completed, the comments sections of the diary cards were reviewed. The parents of 3 children (of 76; 3.9%) had described entire thigh swelling (ETS) within 48 hours of receipt of the fourth dose. None of the 22 children given a fifth dose were reported to have experienced swelling of the entire deltoid (Rennels, 2000).

As stated previously, ETS was observed after a fourth dose of 9 of the 12 DTPa vaccines tested. Trends between groups need to be viewed with caution due to the small number of children followed up per vaccine. However, when all DTPa vaccines were taken together

it could be shown that the rates and severity of fever were not higher in children with ETS than those without; 40% of the cohort with ETS had no pain (although a small percentage of the children experienced severe pain), 40% of the cohort with ETS had no erythema. Swelling had resolved by day 4 in most children and no lasting sequelae were shown.

2.5.5.2.2 Fifth dose study conducted by Scheifele and co-workers

Two hundred and five children having previously received four doses of either DTPa-HBV, DTPa-IPV or DTPa-HBV-IPV in GSK-sponsored trials were administered a fifth dose of DTPa-IPV (Scheifele et al, 2001). Injection site swelling > 50 mm was observed for 20.5% of the vaccinees. None of these subjects had fever or persistent limitation of arm movement. Half of the cases of swelling > 50 mm resolved within 7 days after vaccination and 95% within 14 days.

Children who had local redness or swelling ≥ 10 mm with the third dose at 18 months of age were not more likely to have larger local reactions (≥ 50 mm) after the fifth dose ($p = 1.00$ by McNemar's test).

2.5.5.3 Assessment of large swelling reactions following administration of GSK DTPa vaccines during post-marketing surveillance

The Company performed a first, cumulative review of all cases of injected limb swelling following the administration of DTPa-containing vaccines, reported through passive post marketing surveillance, between the first launch of the vaccine and June 30, 2002. This review was submitted to Regulatory Authorities in the Periodic Safety Update Reports (PSURs) for each of the DTPa-combination vaccines.

In this review, "extensive swelling" was defined as swelling involving an adjacent joint, severe, massive or extensive swelling, or swelling of the whole injected limb. A total of 206 cases of extensive swelling reactions were retrieved from GSK's safety database. The greatest proportion of these cases were reported after a fourth dose of a DTPa-containing vaccine, which is likely to be the reflection of the limited use of some of these vaccines as a fifth dose in children primed with DTPa.

Using the same definition, a second review has been performed covering data accrued up to October 30, 2004. A total of 472 cases of extensive swelling have now been reported (Table 9).

An analysis of the reported cases indicated that they are, in general, similar to what has been observed in the clinical trial setting and therefore present no additional medical concerns. Not observed in clinical trials but reported through post-marketing surveillance were cases of swelling which involved the entire injected limb (i.e. from the shoulder to the wrist or from the thigh to the foot).

The updated reporting frequency of extensive swelling reactions reported through post-marketing surveillance varies from 0.01 per 100,000 doses distributed for DTPa-HBV-IPV to 1.04 per 100,000 doses distributed of DTPa-HBV-IPV/Hib (Table 9). These frequencies are similar to what was previously observed and submitted in the respective PSURs for each of the vaccines. Given the heterogeneity in individual vaccine use (vaccination schedule and history, especially where this concerns previous administration of DTPw), reporting frequencies across vaccines should not be compared.

Table 9. Cases of extensive swelling reactions reported through post-marking surveillance

Vaccine	Doses distributed since launch	Extensive swelling reports	Reporting frequency per 100 000 doses
DTPa	78 894 698	187	0.24
DTPa+HIB	12 209 138	76	0.62
DTPa-IPV	3 759 695	9	0.24
DTPa-HBV	5 806 271	4	0.07
DTPa-IPV+HIB	19 308 559	112	0.58
DTPa-HBV-IPV	8 983 906	1	0.01
DTPa-HBV-IPV+HIB	7 958 783	83	1.04

2.5.6 BENEFITS AND RISKS CONCLUSIONS

It is important to stress that, despite the occurrence of large local reactions, acellular pertussis vaccines induce overall far fewer adverse events than whole-cell vaccines (reviewed in Decker and Edwards, 2000; Jefferson et al, 2003). This is particularly true for common events, such as fever, which occur at much lower frequencies in acellular vaccine recipients.

Local reactions, such as redness and swelling, occur more frequently after booster doses of DTPa in children primed with DTPa vaccine with respect to children primed with DTPw (Halperin et al, 1995; Halperin et al, 1999; Pichichero et al, 1997). Large local reactions, usually defined as either redness and/or swelling ≥ 50 mm in diameter, have been reported following booster doses of licensed vaccines from different manufacturers including GSK (Liese et al., 1999; Halperin et al, 1999; Halperin et al, 2003; Pichichero et al, 1997; Pichichero et al, 2000; Scheifele et al, 2001; Schmitt et al, 1997a; Skowronski et al, 2003), and should thus be considered a class-effect of DTPa-combination vaccines. These reactions are especially frequent in DTPa-primed children after booster doses of DTPa; indeed, they have been observed in approximately 20-50% of children administered a fifth dose of DTPa (Halperin et al, 1999; Halperin et al, 2003; Liese et al, 1999; Scheifele et al, 2001; Skowronski et al, 2003).

Two types of large swelling reactions have been described. The first, reactions which involve a delimited area around the injection site, are the most frequent; the second, reactions which extend diffusely over the injected thigh/upper arm and sometimes the entire limb, are more rare. It should be stressed that, although these reactions are described after DTPa-containing vaccines, they are observed but much less frequently after administration of other vaccines. Indeed, in the US, extensive limb swelling has been reported through the Vaccine Adverse Event Reporting System for a total of 23 different vaccine types (VAERS; Woo et al, 2003). However, extensive limb swelling in the 0-7 year age group was, in 43% of all cases, due to DTPa vaccine, which represented the largest proportion observed for any vaccine.

Attempts to elucidate the mechanisms responsible for large local swelling reactions have been made. A relationship between diffuse swelling reactions of the entire thigh and vaccine antigen content and/or excipients (Rennels et al, 2000) was postulated. Rates of entire thigh swelling was shown to be correlated with diphtheria toxoid content ($p = 0.02$); swelling > 50 mm but not involving the entire thigh was, however, shown to correlate with pertussis toxoid content after dose 4 ($p = 0.03$) and aluminium content after dose 5 ($p = 0.02$). Potential relationships of redness/swelling ≥ 50 mm to antibody levels pre- and post-boost were also examined, with several statistically significant correlations between individual local symptoms and antibody titre being observed (Halperin et al, 2003). However, as no consistent pattern could be developed from these analyses, the role of these factors in the induction of large swelling reactions remains doubtful.

Immunologic pathways have also been explored. The fact that diffuse reactions onset hours, and not minutes after vaccination, argues strongly for a mechamism related to a delayed hypersensitivity response. Early and persistent Th2 responses are elicited after primary vaccination with DTPa vaccine (Rowe et al, 2000), with higher levels of IgE induced with respect to DTPw (Mascart, 2004). However, there has been no association found between levels of circulating IgE and booster reactogenicity despite increases in IgE levels after the booster dose (Holt, personal communication). Moreover, prophylactic treatment with antihistamines has been shown to have no effect on the frequencies of local redness or swelling (Tam and Scheifele, 1996). Skin tests have shown a correlation between redness ≥ 50 mm and test positivity for DT and Pa antigens, but no such correlation was found for swelling ≥ 50 mm (Scheifele et al, 2001). In addition, in this same trial, rates of swelling or redness were not influenced by a history of allergy/atopy. One evident intrinsic factor which would predispose the vaccinee towards large local reactions has therefore not been determined at present.

Pragmatically, large local reactions after a fourth dose of DTPa would not appear to be predictive of reactions after a fifth dose. Clinical data indicates that children who had larger local redness or swelling after a fourth dose at 1-2 years were no more likely to have redness or swelling ≥ 50 mm after a fifth dose at 4-6 years (Scheifele et al, 2001; and studies 208355/118 and 208355/120). In the MAPT, none of three children who had swelling of the entire thigh after the fourth dose reported swelling of the entire thigh after the fifth dose (Rennels et al, 2000).

A total of 481 large swelling reactions have been reported in the GSK sponsored clinical trials where they were solicited. In general, large swelling reactions have not been

reported to be associated with higher incidences of fever or severe pain. In their assessments, the investigators have reported that the large swelling reactions resolved for all subjects (with the exception of one case for which the outcome was unknown). The mean time to resolution was approximately 4 days. In these trials, only one serious adverse event has been reported in conjunction with a large swelling reaction; a child enrolled in study 213503/049 experienced diffuse swelling on the day after vaccination and was hospitalised the next day. A diagnosis of cellulitis was made and the child was treated with antibiotics. The reaction was reported as resolved after 4 days.

When parents of children immunised with a fifth dose of DTPa were asked whether injection site reactions were an acceptable part of routine immunisation, 67% of the parents responded that they were very acceptable (Halperin et al, 2003). However, as highlighted by these authors, "this still leaves 33% who do not think that they were a very acceptable part". They conclude that "the injection site reactions have a potential to put the current high rates of vaccine uptake at risk and add to the increased anti-vaccination sentiment observed in some areas".

GSK considers that it is important to include information on large swelling reactions in the SPC and PIL of all DTPa-combination vaccines. The Company feels that both the prescribers and parents should be informed that these reactions are an expected side effect of DTPa booster administration. The Company seeks to avoid wording which may inadvertently lead to a decrease in compliance with booster recommendations, especially as these large local reactions are transient and of limited medical consequence.

GSK would like to ensure similar wording across all *Infanrix*-line products, given that there are no relevant clinical differences between the vaccines when they are used as a fourth dose during the second year of life, or when they are used as a fourth/fifth dose at 4-6 years of age. CIOMS frequency classifications have been used for all events.

In agreement with the CHMP, Section 4.8 of the SPCs for *Infanrix hexa* and *Infanrix penta* has been amended as follows: "swelling" identified as very common has been amended to "local swelling at the injection site (≤ 50 mm)", "local swelling at the injection site (> 50 mm)" has been added and identified as occurring commonly after booster immunisation, "diffuse swelling of the injected limb, sometimes involving the adjacent joint" has been identified as being uncommon. "Swelling of the entire injected limb" has been added as occurring during post-marketing surveillance. A supplementary sentence further describing large swelling reactions has also been included: "Children primed with acellular pertussis vaccines are more likely to experience swelling reactions after booster administration in comparison with children primed with whole cell vaccines. These reactions resolve over an average of 4 days." It is proposed that the PI for *Infanrix-Hib* also be modified accordingly.

In countries where *Infanrix* and *Infanrix-IPV* are licensed for use as a second booster dose, the supplementary sentence will read: "Children primed with acellular pertussis vaccines are more likely to experience swelling reactions after booster administration in comparison with children primed with whole cell vaccines. Local swelling at the injection site (> 50 mm) and diffuse swelling may be more frequent (very common and common,

respectively) when the booster dose is administered between 4 and 6 years. These reactions resolve over an average of 4 days."

2.5.7 LITERATURE REFERENCES

Blennow M and Granström M. Adverse reactions and serologic response to a booster dose of acellular pertussis vaccine in children immunized with acellular or whole-cell vaccine as infants. Pediatrics 1989;84(1):62-67.

Decker MD, Edwards KM, Steinhoff MC, et al. Comparison of 13 acellular pertussis vaccines: adverse reactions. Pediatrics 1995; 96 (suppl): 557-566.

Decker MD, Edwards KM. Acellular pertussis vaccines. Pediatr Clin North Am. 2000; 47:309-335.

Halperin SA, Mills E, Barreto L, Pim C, Eastwood BJ. Acellular pertussis vaccine as a booster dose for seventeen- to nineteen-month-old children immunized with either whole cell or acellular pertussis vaccine at two, four and six months of age. Pediatr Infect Dis J 1995; 14:792-797.

Halperin SA,Eastwood BJ, Barreto L et al. Adverse reactions and antibody response to four doses of acellular pertussis vaccine combined with diphtheria and tetanus toxoids in the first 19 months of life. Vaccine 1996, 14: 767-772

Halperin SA, Scheifele D, Barreto L, et al. Comparison of a fifth dose of a five-component acellular or a wholde cell pertussis vaccine in children four to six years of age. Pediatr Infect Dis J. 1999; 18:772-779.

Halperin SA, Scheifele D, Mills E. et al. Nature, evolution, and appraisal of adverse events and antibody response associated with the fifth consecutive dose of a five-component acellular pertussis-based combination vaccine. Vaccine 2003; 21:2298-2306.

Jackson LA, Starkovich P, Froeschle J, et al. Prospective assessment of the safety of the fifth consecutive dose of Tripedia dtap vaccine. Presented as the 42nd ICAAC meeting, September 27-30, 2002 San Diego, CA. Abstract G-1215.

Jefferson T, Rudin M, DiPietrantonj C. Systematic review of the effects of pertussis vaccines in children. Vaccine 2003; 21:2003-2014.

Liese JG, Stojanov S, Zink TH, et al. Safety and immunogenicity of Biken acellular pertussis vaccinat in combination with diphtheria and tetanus toixoid as a fifth dose at four to six years of age. Pediatr Infect Dis J 2001; 20:981-988.

Mascart F. Infant immune responses to pertussis infection and vaccines. Presented at the 1st International Neonatal Vaccination Workshop, March 2-4, 2004 Maclean, VA.

Noble GR, Bernier RH, Esber EC, et al. Acellular and whole-cell pertussis vaccines in Japan. Report of a visit by US scientists. JAMA 1987;257(10):1351-1356.

Pichichero ME, Deloria MA, Rennels MB, et al. A safety and immunogenicity comparison of 12 acellular pertussis vaccines and one whole-cell pertussis vaccine given as a fourth does in 15- to 20-month-old children. Pediatrics 1997; 100:772-788.

Pichichero ME, Edwards KM, Anderson EL et al. Safety and immunogenicity of six acellular pertussis vaccines and one whole-cell pertussis vaccine given as a fifth dose in four- to six-year old children. Pediatrics 2000;105(1), www.pediatrics.org/cgi/content/full/105/1/e11

Rennels MB, Deloria MA, Pichichero M et al. Extensive swelling after booster doses of acellular pertussis-tetanus-diphtheria vaccines. Pediatrics 2000;105 (1), www.pediatrics.org/cgi/content/full/105/1/ e12

Rowe J, Macaubas C, Monger TM, et al. Antigen-specific responses to diphtheria-tetanus-acellular pertussis vaccine in human infants are initially Th2 polarized. Infect Immun. 2000; 68:3873-3877.

Scheifele D, Bjornson G, Barreto L, Meckison W, Guasparini R. Controlled trial of *Haemophilus influenzae* type B diphtheria toxoid conjugate combined with diphtheria, tetanus and pertussis vaccine, in 18-month old children, including comparison of arm versus thigh injection. Vaccine 1992; 10:455-460.

Scheifele DA, Halperin SA, Ferguson AC. Assessment of injection site reactions to an acellular pertussis-based combination vaccine, including novel use of skin tests with vaccine antigens. Vaccine 2001; 19:4720-4726.

Schmitt H-J, Müschenborn S, Wagner S, et al. Immunogenicity and reactogenicity of a bicomponent and a tricomponent acellular pertussis-diphtheria-tetanus (DTaP) vaccine in primary immunization and as second year booster: a double-blind, randomized trial. Int J Infect Dis 1996; 1:6-13.

Schmitt H-J, Beutel K, Schuind A, et al. Reactogenicity and immunogenicity of a booster dose of a combined diphtheria, tetanus, and tricomponent acellular pertussis vaccine at fourteen to twenty-eight months of age. J Pediatr 1997a;130:616–23

Schmitt H-J, Wirsing von König CH, Zepp F, et al. Immunogenicity and reactogenicity of HbOC vaccine administered simultaneously with acellular pertussis vaccine (DTaP) into either arms or thighs of infants. Infection 1997b; 25:298-302.

Tam T, Scheifele D. Local adverse reactions following a booster dose of acellular pertussis DT vaccine: lack of effect of laratadine prophylaxis. Presented at the 36th ICAAC meeting, September 15-18, 1996 New Orleans, LO. Abstract G-104.

Woo EJ, Berwen DR, Gatumu SNM, Ball R and the VAERS Working Group. Extensive limb swelling after immunization: reports to the Vaccine Adverse Event Reporting System. Clin Infect Dis 2003; 37:351-358.

2-7 - 4 Summary of Clinical Safety

Document 1

CONFIDENTIAL

Module 2.7 : Clinical Summary

2.7.4 SUMMARY OF CLINICAL SAFETY

TABLE OF CONTENTS

PAGE

2.7.4 SUMMARY OF CLINICAL SAFETY 1
2.7.4.1 Exposure to the Drug 3
2.7.4.1.1 Overall Safety Evaluation Plan and Narratives of Safety Studies 3
2.7.4.1.2 Overall Extent of Exposure 37
2.7.4.1.3 Demographic and Other Characteristics of Study Population 37
1.7.4.2 Adverse Events 37
1.7.4.2.1 Analysis of Adverse Events 37
2.7.4.2.1.1 Common Adverse Events 40
2.7.4.2.1.2 Deaths 50
2.7.4.2.1.3 Other Serious Adverse Events 50
2.7.4.2.1.4 Other Significant Adverse Events 50
2.7.4.2.1.5 Analysis of Adverse Events by Organ System or Syndrome 50
2.7.4.2.2 Narratives 50
2.7.4.3 Clinical Laboratory Evaluations 50
2.7.4.4 Vital Signs, Physical Findings, and Other Observations Related to Safety 50
2.7.4.5 Safety in Special Groups and Situations 50
2.7.4.5.1 Intrinsic Factors 50
2.7.4.5.2 Extrinsic Factors 51
2.7.4.5.3 Drug Interactions 51
2.7.4.5.4 Use in Pregnancy and Lactation 51
2.7.4.5.5 Overdose 51
2.7.4.5.6 Drug Abuse 51
2.7.4.5.7 Withdrawal and Rebound 51
2.7.4.5.8 Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability 51
2.7.4.6 Postmarketing Data 51

Document 1

CONFIDENTIAL

LIST OF TABLES

		PAGE
Table 1	The Infanrix range of Pa based combination vaccines	3
Table 2	Studies pertinent to the variation (by vaccine dose) and the Infanrix range vaccine or vaccines involved in each study	4
Table 3	Study cohorts by dose and study – vaccinees receiving an Infanrix range vaccine	38
Table 4	Reports of swelling, pain and fever in vaccinated subjects	41
Table 5	Incidence of extensive/large swelling reactions, by dose: all types combined	42
Table 6	1st booster dose – Incidence of actively solicited large swelling reaction reports (all types combined, including unspecified types) following vaccination with a Pa containing vaccine, by study	43
Table 7	Reaction reports by study, vaccine and type: 1st booster dose in the second year of life after Pa priming	43
Table 8	Large swelling reaction reports of all types by vaccine after 1st booster dose in the 2nd year of life	44
Table 9	Reaction reports by vaccine and type – 1st booster dose at 4-6 years after Pa administered at 3, 5, 11/12 months – study 213503/045	44
Table 10	Reaction reports by vaccine and type – 2nd booster dose at 4-6 years after Pa priming and boosting in the first two years of life – study 213503/046	45
Table 11	Reaction reports by vaccine dose and schedule – 1st booster dose in the 2nd year of life, vaccination at 4-6 years after 3, 5, 11/12 months and 2nd booster dose at 4-6 years	45
Table 12	Relative proportions of reported Type 1 versus Type 2 & 3 reactions – reaction reports by vaccine and swelling types	46
Table 13	Incidence and characteristics of reported large or extensive swelling reactions, by vaccine dose and reaction type	47
Table 14	Solicited reports of swelling reactions: all swellings and large or extensive swellings	48
Table 15	Solicited reports of swelling reactions, all swellings and large/extensive swellings – grade 3 pain, fever and impairment, by dose	49
Table 16	Reported frequency per 100,000 doses of "extensive reactions" by vaccine	52

2.7.4.1 Exposure to the Drug

2.7.4.1.1 Overall Safety Evaluation Plan and Narratives of Safety Studies

Eighteen clinical trials and a review of data obtained through post-marketing surveillance are submitted in support of the proposed update to Section 4.8 of the Summary of Product Characteristics (SPC).

The clinical studies presented comprise all reported booster vaccination studies that have:

- Involved any of the *Infanrix* range of GSK Biologicals combination vaccines (all of which contain an acellular pertussis component) and:
- Either actively solicited the reporting of large or extensive swelling reactions, or had a protocol defined procedure for follow up of any large or extensive swelling reactions that were reported to the investigator.

Table 1 lists the vaccines that collectively make up the *Infanrix* range.

The convention adopted throughout this summary, and in the individual clinical study reports is that when abbreviated descriptions (e.g. DTPa-IPV/Hib) are used for the vaccines, a hyphen "-" indicates that the vaccine components are formulated together, and a slash "/" indicates that they are mixed immediately prior to administration. When vaccines are given separately, but concomitantly, this is indicated by a plus sign "+".

Table 1 The Infanrix range of Pa based combination vaccines

Vaccine	Components	Short form
Infanrix	Diphtheria-tetanus-acellular pertussis	DTPa
Infanrix-Hib	Diphtheria-tetanus-acellular pertussis/*Haemophilus influenzae* type b	DTPa/Hib
Infanrix-HepB	Diphtheria-tetanus-acellular pertussis-hepatitis B	DTPa-HepB
Infanrix-IPV (Infanrix tetra)	Diphtheria-tetanus-acellular pertussis-inactivated polio	DTPa-IPV
Infanrix-IPV/Hib	Diphtheria-tetanus-acellular pertussis-inactivated polio/ *Haemophilus influenzae* type b	DTPa-IPV/Hib
Infanrix penta	Diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated polio	DTPa-HBV-IPV
Infanrix hexa	Diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated polio/*Haemophilus influenzae* type b	DTPa-HBV-IPV/Hib

Table 2 lists the clinical studies that are pertinent to the variation (by vaccine dose) and the *Infanrix* range vaccine or vaccines involved in each study. All of the vaccines that make up the range except one (*Infanrix HepB*, DTPa-HepB) were implicated in at least one of the reported clinical studies that actively solicited large or extensive swelling reactions after a booster dose. All of the pertussis vaccine doses that preceded the booster dose administered during the course of the study had been with acellular pertussis.

Document 1

CONFIDENTIAL

Table 2 Studies pertinent to the variation (by vaccine dose) and the Infanrix range vaccine or vaccines involved in each study

Study code	Vaccine(s)	Country
Studiesinvolving a first booster dose in the 2nd year of life after a 3-dose primary course with a Pa based combination vaccine in the first six months of life (Large swelling reactions actively solicited in all of these studies)		
208108/076	DTPa/Hib DTPa	Australia
213503/043	DTPa-IPV/Hib	Lithuania
213503/049	DTPa-IPV/Hib	Spain
217744/058	DTPa-HBV-IPV/Hib DTPa-IPV/Hib	Germany
217744/059	DTPa-HBV-IPV/Hib	Switzerland
217744/061	DTPa-HBV-IPV DTPa	USA
217744/062	DTPa-HBV-IPV/Hib	The Philippines
217744/065	DTPa-HBV-IPV/Hib	Germany
217744/066	DTPa-HBV-IPV/Hib	Germany
217744/074	DTPa-HBV-IPV/Hib DTPa-IPV/Hib	Germany
217744/095	DTPa-HBV-IPV/Hib	Germany
404286/006	DTPa-HBV-IPV/Hib	Germany
455697/001	DTPa-IPV/Hib	Lithuania
711202/008	DTPa-HBV-IPV/Hib	Germany
Study involving a 4th dose of Pa containing vaccine in children aged 4-6 years who had previously been vaccinated at 3, 5 and 11-12 months of age (Large swelling reactions actively solicited in this study)		
213503/045	DTPa-IPV DTPa	Italy & Sweden
Studies involving a 2nd booster dose of Pa containing vaccine in children aged 4-6 years who had previously received 4 doses of Pa containing vaccine in the first two years of life (Large swelling reactions actively solicited only in 213503/046)		
208355/118	DTPa	Germany
208355/120	DTPa	Germany
213503/046	DTPa-IPV DTPa	Australia

In all of the studies the characteristics of what were to be considered to be large or extensive swelling reactions were defined in the protocol. With the exception of 455697/001 they were swelling with longest diameter > 50 mm, noticeable diffuse swelling, noticeable increase in limb circumference) were defined in the protocol. For 455697/001 they were swelling with longest diameter > 50 mm or an increase of the limb circumference of > 50 mm as compared to a pre-vaccination measurement.

For all studies except 208355/118 and 208355/120 parents or guardians identifying such swellings were to contact the investigator and arrange for an examination. For studies 208355/118 and 208355/120 the protocol specified that parents or guardians were to contact the investigator immediately if the subjects manifested any signs or symptoms that raised their concern, but large swellings were not specifically solicited. Parents

spontaneously contacting the investigator to report extensive local swelling were asked to present the child for an examination.

Details regarding the follow up of large swellings can be found in Section 2.7.4.2.1.

Whilst the protocol definition of what constituted a large or extensive swelling reaction was the same for almost all of the studies, the phraseology used when referring to such reactions has not always been the same. The following synonyms (all of which apply to events of the same general nature) have been used, and may appear in this clinical summary: "large swelling reactions", "extensive swelling reactions" and "large or extensive" swelling reactions.

Although, in 16 of the 18 studies, the reporting of large or extensive swelling reactions was actively solicited, the investigation of such reactions was a study objective in only one (217744/074). The study objective, or objectives, for each study is/are summarised in each individual study narrative.

In study 208355/118, additional subjects were enrolled to receive commercial vaccines other than the *Infanrix* range of vaccines (*Boostrix* or adult formulation Td vaccine). Also, in some studies vaccinees received experimental vaccines. All vaccines administered, whether commercial or experimental, are identified in the narrative summaries that follow. All large or extensive swelling reaction reports are described in the full clinical study reports, irrespective of the vaccine administered. In the narrative summaries only the reports that follow vaccination with the *Infanrix* range of vaccines, other commercially available vaccines or experimental vaccines the results from which are relevant for the *Infanrix* range, are noted. In the summary tables only the reports for the *Infanrix* range are included. The individual subject data that are provided in the Appendix include data from events that followed vaccination with all of the commercial vaccines administered during the course of the studies.

All of the studies were conducted according to Good Clinical Practice guidelines in force at the time of their initiation and according to the Declaration of Helsinki. Ethics Committee approval was obtained for all protocols. Written informed consent was obtained from the parents or guardians of subjects prior to enrolment.

The narratives have been restricted to those aspects of the studies that are relevant to the investigation of large or extensive swelling reactions and to the analysis of their clinical significance. Specifically, they address:

i). The incidence of all solicited swelling reactions. (Reactions were recorded, by parents or guardians, on the symptom sheets used to document solicited adverse events. They included smaller discrete reactions that did not meet the protocol definition of a large or extensive swelling). Also documented is the incidence of redness, pain and fever following vaccination.

ii). The incidence of reported reactions meeting the protocol definition of large or extensive swelling reactions and, within the cohorts for which such reactions were reported, the characteristics of the swellings, any associated pain or physical impairment and the incidence of fever. Any other pertinent information is also summarised.

Document 1

CONFIDENTIAL

Narrative descriptions of studies: first booster in the second year of life after 3 dose primary course in the first six months of life with Pa containing combination vaccine.

208108/076 (Hib-076) (Australia)

Design: an open phase III booster study with two parallel groups in a 1:3 allocation.

Group 1 received DTPa and unconjugated PRP given concomitantly.
Group 2 received DTPa/Hib.

Objectives: the primary objectives of the study were the assessment of immune memory and immune response. Assessment of reactogenicity was one of the secondary objectives.

Population: healthy children aged 12 to 18 months, previously vaccinated at 2, 4 and 6 months with DTPa-HBV-IPV/Hib combination vaccine.

Administration: vaccines were administered by IM injection into the deltoid. For the group receiving two vaccines, these were administered in opposite limbs.

Solicited signs and symptoms: solicited local symptoms included swelling, pain and redness. Solicited general symptoms included fever.

Follow up of extensive swelling reactions: the reporting of extensive swelling of the vaccinated limb was actively solicited.

Results:

Reports of pain and redness associated with any injection site swelling including swellings not meeting the protocol definition of "large or extensive swelling", and reports of fever in vaccinated subjects

A total of 289 subjects (70 from group 1 and 219 from group 2) were vaccinated in this study; all but one were included in the ATP cohort for the analysis of safety. Compliance for the return of symptom sheets was ! 95%.

Injection site swelling was recorded at the site of injection of the DTPa vaccine in 40 subjects (58.0%) from group 1 and in 118 of the vaccinees from group 2 (53.9%).

Pain at the injection site of the Pa containing vaccines was reported in 31/69 (44.9%) and 90/219 (41.1%) of instances for groups 1 and 2, respectively. Grade 3 pain (cried when limb was moved/spontaneously painful) was noted for one vaccinee (1.4%) from group 1 and two vaccinees (0.9%) from group 2.

Redness was reported for 69.6% of vaccinees from group 1 and 65.6% of subjects from group 2.

Fever (and other symptoms) was recorded over 8 days in this study. There were 15 reports of fever (rectal temperature ! 38.0°C, temperature by other routes ! 37.5°C) from the ATP cohort for the analysis of reactogenicity in group 1 (22.7%). There were 69

Document 1

CONFIDENTIAL

reports of fever (33.2%) from group 2. Grade 3 fever (rectal temperature ! 39.6°C, temperature by other routes ! 39.1°C) was reported for 1 (1.5%) and six (2.9%) subjects, respectively.

Extensive swelling
Extensive swelling reports were to be completed only for those reactions occurring at the site of injection of DTPa or DTPa/Hib vaccines. Reports were completed for 30 subjects, 12/70 from group 1 (17.1%) and 18/219 from group 2 (8.2%). From group 1, all of the swellings were recorded as being local, not involving adjacent joints. For group 2, 15 swellings were noted as local, not involving adjacent joints, one was categorised as diffuse, not involving adjacent joints and two were recorded as involving at least one adjacent joint.

For all reports combined, the recorded day of onset ranged from day 0 to day 3. Duration of the extensive swelling was noted as ranging from 1-4 days for group 1 and 2-7 days for group 2.

Mild pain was reported in four instances from group 1, mild or moderate pain in four instances from group 2. There were no reports of severe pain. Functional impairment (which was scored as mild) was noted in only one subject (from group 2).

The diameter of locally discrete swellings ranged from 45-90 mm for group 1 and 40-80 mm for group 2. Of tbe reports for group 1, 10 recorded redness and 11 induration. Among the 18 reports for group 2 there were 16 of redness and 17 of induration.

The recorded increase in circumference of the vaccinated limb versus the opposite limb ranged from 5-50 mm in group 1 and 6-30 mm in group 2.

There was no fever associated with any of the extensive swelling reports.

All of the large swelling reactions resolved.

213503/043 (DTPa-IPV-043) (Lithuania)

Design: a double blind, randomised phase III booster study with two groups in a balanced 1:1 allocation.

> Group 1 received DTPa-IPV vaccine mixed with conjugated Hib vaccine. The tetanus toxoid used as carrier protein for the Hib vaccine was manufactured by Human Co, Hungary (Hib-TH).
> Group 2 received DTPa-IPV vaccine mixed with conjugated Hib vaccine. The tetanus toxoid used as carrier protein for the Hib vaccine was manufactured by Chiron-Behring GmbH, Marburg, Germany (Hib-TB).

Objectives: the primary objective of the study was to demonstrate, in terms of immunogenicity of the Hib antigen, that Hib-TH was equivalent to Hib-TB when mixed with DTPa-IPV and given as a booster dose. Assessment of reactogenicity and safety of the study vaccines was one of the secondary objectives of the study.

Population: healthy children aged 17 to 19 months who had previously received three doses of DTPa-IPV/Hib at 3, 4.5 and 6 months of age.

Administration: vaccines were administered by IM injection into the anterolateral thigh.

Solicited signs and symptoms: solicited local symptoms included swelling, pain and redness. Solicited general symptoms included fever.

Follow up of extensive swelling reactions: the reporting of extensive swelling was actively solicited.

Results:

Reports of pain and redness associated with any injection site swelling including swellings not meeting the protocol definition of "large or extensive swelling", and reports of fever in vaccinated subjects

A total of 200 subjects were vaccinated, 102 from group 1 and 98 from group 2. One-hundred-and-ninety-nine were included in the ATP cohort for the analysis of safety, 101 from group 1 and 98 from group 2. Compliance for the return of symptom sheets was 99% for group 1 and 100% for group 2.

Injection site swelling at the site of injection was reported for 39/101 subjects from group 1 (38.6%). For group 2, there were 49 reports of swelling from 98 subjects (50.0%).

In the same cohort pain was reported for 55.4% (56/101) and 61.2% (60/98) subjects, respectively. Grade 3 pain (subject cried when limb was moved/spontaneously painful - prevented normal activity) was reported for four subjects in group 1 (4.0%) and 11 subjects in group 2 (11.2%).

Redness was reported for 58.0% of vaccinees from group 1 and 66.3% of vaccinees from group 2.

Fever (rectal temperature ! 38.0°C, temperature by other routes ! 37.5°C) was reported in 29/101 subjects in group 1 (28.7%) and 38/98 subjects in group 2 (38.8%). There were two reports (both from group 2) of grade 3 fever (rectal temperature ! 39.6°C, axillary or oral temperature ! 39.1°C).

Extensive swelling

Extensive swellings were reported for eight subjects from group 1 (7.8% of the vaccinated cohort) and seven subjects from group 2 (7.1%). For two subjects in each group, the category of swelling was not recorded. In all other cases the swellings were recorded as large local reactions. No diffuse swellings were reported. Recorded day of onset ranged from day one to day three. The reported duration of the extensive swelling was from 1-7 days, with the exception of one report for group 1, for which the duration was noted as 17 days.

Six reports from group 1 and five from group 2 noted pain. There were no reports of grade 3 pain associated to any of the extensive swellings and no reports of functional impairment.

The diameter of the swellings ranged from 60 to 90 mm for group 1 and 60 to 150 mm for group 2. Redness was observed in all cases, and induration reported in three instances for group 1 and four for group 2. The difference in circumference of the vaccinated versus the opposite limb ranged from 5 to 50 mm.

Fever was noted in 3/8 subjects for whom swelling reports were completed in group 1 (37.5%) and 1/7 subjects from group 2 (14.2%). No grade 3 fever was reported in any of these subjects.

In one case the outcome was unknown. All other large swelling reactions resolved.

213503/049 (DTPa-IPV-049) (Spain)

Design: an open, phase IV booster vaccination study with all subjects receiving DTPa-IPV/Hib vaccine.

Objectives: the primary objective of the study was to evaluate the response to the PRP component after boosting and following primary vaccination regimes in which DTPa-HBV-IPV/Hib vaccine had been given either with or without concomitant administration of meningococcus type C conjugate vaccine (*Meningitec* - Wyeth). Assessment of the safety and reactogenicity of the vaccine was a secondary objective.

Population: healthy children aged 17 to 20 months who had been previously vaccinated with DTPa-HBV-IPV/Hib at 2, 4 and 6 months of age either given concomitantly with *Meningitec* or in a staggered regime in which *Meningitec* was given at 3, 5 and 7 months of age.

Administration: the vaccine was administered by IM injection into the anterolateral thigh using a 1 inch needle.

Solicited signs and symptoms: solicited local symptoms included swelling, pain and redness. Solicited general symptoms included fever.

Follow up of extensive swelling reactions: reporting of large injection site swellings was actively solicited.

Results:

Reports of pain and redness associated with any injection site swelling including swellings not meeting the protocol definition of "large or extensive swelling", and reports of fever in vaccinated subjects

A total of 344 subjects were vaccinated in this study: 341 were eligible to be included in the ATP cohort for the analysis of safety. The analysis of safety was performed on the total vaccinated cohort. Compliance for the return of symptom sheets was 99.4%.

Injection site swelling was reported for 141/344 subjects in the total vaccinated cohort (41.0%). Pain was noted in 160/344 (46.5%). In 13 instances (3.8% of the cohort) pain was recorded as grade 3 (cried when limb was moved/spontaneously painful). Redness was reported for 173 vaccinees (50.3%).

Document 1

CONFIDENTIAL

There were 57 reports of fever (rectal temperature ! 38.0°C, temperature by other routes ! 37.5°C) (16.6%). Five reports (1.5%) were of fever with a rectal temperature > 39.5°C.

Extensive swelling
Large injection site reactions were reported for 21 subjects (6.1% of the vaccinated cohort). Nineteen of the swellings were categorised as local swellings, not involving an adjacent joint and two were noted as diffuse, not involving an adjacent joint.

All the events were noted as starting within two days of vaccination. Recorded duration of the extensive swelling ranged from 1-15 days. (The duration was seven days or less for 13 of the events and the majority had resolved within four days.)

Pain was noted in 16 of the 21 reports (76.2%), and was recorded as grade 3 in two (9.5%). In both of these latter cases functional impairment was also present. In total, four of the reports noted functional impairment, graded 3 in two. (See the summary below regarding one swelling reaction reported as a serious adverse event).

The diameter of discrete, measurable swellings ranged from 50-200 mm. The circumference of the limbs was determined, or recorded, in only two subjects. All except one report observed redness and 11 noted induration.

Fever was reported in only two subjects. None of the large swelling events were associated with fever > 39.5°C.

One subject demonstrated grade 3 pain and grade 3 functional impairment. This event was reported as a serious adverse event. Two days after vaccination the child was hospitalised and a diagnosis of cellulitis, causally related to vaccination, was made. There was no fever. The reaction had resolved by the fourth day after vaccination and the subject was discharged from hospital.

All other large swelling reactions also resolved.

217744/058 (DTPa-HBV-IPV-058) (Germany)

Design: an open, phase III, randomised booster study with three groups in a 3:1:1 ratio.

Group 1 received DTPa-HBV-IPV/Hib vaccine.
Group 2 received DTPa-IPV/Hib vaccine.
Group 3 received DTPa-IPV/Hib vaccine concomitantly with HBV vaccine, *Engerix B*.

Objectives: the primary objective of the study was to demonstrate that DTPa-HBV-IPV/Hib vaccine was at least as safe as DTPa-IPV/Hib vaccine administered concomitantly with HBV vaccine in terms of severe (grade 3) solicited symptoms after booster vaccination.

Population: healthy children aged 12 to 18 months that had previously been vaccinated at 3, 4 and 5 months either with DTPa-HBV-IPV/Hib vaccine or with DTPa-IPV/Hib vaccine given concomitantly with HBV.

Administration: vaccines were administered by deep IM injection into the anterolateral thigh.

Solicited signs and symptoms: solicited local symptoms included swelling, pain and redness. Solicited general symptoms included fever.

Follow up of extensive swelling reactions: the reporting of extensive swelling was actively solicited.

Results:

Reports of pain and redness associated with any injection site swelling including swellings not meeting the protocol definition of "large or extensive swelling", and reports of fever in vaccinated subjects

A total of 1149 subjects (693 for group 1, 226 for group 2 and 230 for group 3) were enrolled into the study and vaccinated. 1138 subjects were included in the ATP cohort for the analysis of safety. (In the ATP cohort there were 688 subjects from group 1, 223 from group 2 and 227 from group 3). Compliance with the return of symptom sheets was > 99.0%.

Injection site swelling at the site of injection of one of the Pa containing vaccines was reported for 317/1138 subjects (27.9%): 210/688 subjects from group 1 (30.5%) and 107/450 subjects from groups 2 and 3 combined (23.8%). In the same ATP cohort pain at the site of injection with a Pa combination vaccine was reported for 31.1% of subjects overall: 214/688 subjects from group 1 (31.1%) and 140/450 (31.1%) from groups 2 and 3 combined. Grade 3 pain (cried when limb was moved or spontaneously painful) was reported in 60/1138 vaccinees (5.3%).

Redness at the site of injection of one of the combination vaccines was reported for 512/1138 subjects (45.0%): 48.0% from group 1 and 42.9% from the combined groups 2 and 3.

Fever (rectal temperature ! 38.0°C, temperature by other routes ! 37.5°C) was noted in 40.2% (458/1138) of subjects from the ATP cohort: 289/688 (42.0%) from group 1, 90/223 subjects (40.3%) from group 2 and 79/227 (34.8%) from group 3). In 35 subjects (3.1%) it was noted as> 39.5°C rectally (temperature by other routes > 39°C).

Extensive swelling

Extensive swelling reports were completed for 29 subjects (2.5% of the total vaccinated cohort). There were 13 reports from the 693 subjects in the cohort for group 1 (1.9%), 10 reports from 226 subjects for group 2 (4.4%) and six reports from 230 subjects for group 3 (2.6%). All of the swellings reported from group 3 were at the site of injection of DTPa-IPV/Hib vaccine.

Eight of the swellings reported from group 1 were typed 1 (local swelling around the injection site, not involving adjacent joints) (61.5% of extensive swelling reports), five (38.5%) were typed 2 (diffuse swelling, not involving adjacent joints). From groups 2 and 3 combined, seven were recorded as type 1 (43.8%), seven as type 2 and two (12.5%) as type 3 (swelling involving at least one adjacent joint).

For all of the reports combined, the day of onset ranged from day 0 to day 2. The recorded duration of extensive swelling ranged from 1 to 9 days.

Sixteen of the 29 cases (55.2%) were reported to have associated pain. Eight reports of pain were from group 1 (61.5% of the group 1 subjects for which a swelling report was completed). Eight were from groups 2 and 3 combined (50.0% of these combined groups). In five reports (of which three were from group 1), pain was scored as grade 3. Functional impairment was reported for eight subjects, seven of which were from group 1. Four of the reports noting impairment also recorded grade 3 pain. In two (both from group 1) both pain and impairment were graded 3.

The two reported type 3 swellings were both from group 2.

The diameter of large local swellings ranged from 35 to 250 mm (50-250 mm for group 1, 35-100 mm for group 2 and 50-250 mm for group 3). Redness was reported in 24 cases (of which 10 were from group 1) and induration in 13 (seven from group 1). The measured difference in limb circumference ranged from 0 to 40 mm.

Fever was reported in thirteen instances (44.8%). Six of these were from group 1. There were four reports of fever > 39.5°C of which one was from group 1 and three from groups 2 and 3 combined.

All large swelling reactions resolved.

217744/059 (DTPa-HBV-IPV-059) (Switzerland)

Design: an open phase III booster study with all subjects receiving DTPa-HBV-IPV/Hib vaccine.

Objectives: the primary objective of the study was the assessment of immune response. Safety and reactogenicity assessment was a secondary objective.

Population: healthy children aged 12 to 18 months who had previously been primed either with DTPa-HBV-IPV/Hib vaccine or with DTPa-IPV/Hib vaccine given concomitantly with HBV.

Administration: vaccine was administered by deep IM injection into the thigh.

Solicited signs and symptoms: solicited local symptoms included swelling, pain and redness. Solicited general symptoms included fever.

Follow up of extensive swelling reactions: the reporting of extensive swelling of the vaccinated limb was actively solicited

Results:

Reports of pain and redness associated with any injection site swelling including swellings not meeting the protocol definition of "large or extensive swelling", and reports of fever in vaccinated subjects

A total of 443 subjects were vaccinated in this study and 440 included in the ATP cohort for the analysis of safety. Compliance for the return of symptom sheets was 99.8%.

Injection site swelling was reported for 158 subjects (35.9%).

Pain was reported for 171/440 subjects (38.9%) and grade 3 pain (cried when limb was moved/spontaneously painful) for 28 (6.4%).

Redness was reported for 233/440 subjects (53.0%).

Fever (rectal temperature ! 38.0°C, temperature by other routes ! 37.5°C) was noted in 207/440 subjects (47.0%). There were 20 reports (4.5% of the cohort) of grade 3 fever (rectal temperature > 39.5°C, axillary temperature > 39.0°C)

Extensive swelling
Extensive swelling reports were completed for 15 subjects (3.3% of the vaccinated cohort). Thirteen reports noted type 1 swellings (local swelling around the injection site, not involving an adjacent joint) and two type 2 (diffuse swelling not involving an adjacent joint).

Day of onset ranged from 0 to 3 days and the recorded duration of the extensive swelling from 1 to 8 days.

In nine of the reports (60.0%) swelling was associated with pain. There were no reports of grade 3 pain. Functional impairment was noted in three reports (none recorded as severe). Two of the three reports of functional impairment also noted pain.

The diameter of local swellings ranged from 40 to 140 mm. The presence of redness was noted in all reports, and induration in 12 subjects. The measured difference in limb circumference ranged from 0 to 30 mm.

Fever was recorded in five reports (33.3%). Fever > 39.5°C was noted in one subject.

All large swelling reactions resolved.

217744/061 (DTPa-HBV-IPV-061) (USA)

Design: a randomised, single blinded, controlled phase II booster study with 2 groups in a balanced 1:1 ratio.

Group 1 received DTPa vaccine with Aventis-Pasteur's *OmniHIB* given concomitantly.
Group 2 received DTPa-HBV-IPV vaccine with *OmniHIB* given concomitantly.

Objectives: the primary objective was to evaluate the safety and reactogenicity of the booster dose of DTPa-HBV-IPV compared with DTPa when the vaccines were co-administered with *OmniHIB*.

Population: healthy children aged between 15 and 18 months previously vaccinated in a 3 dose primary course with DTPa-HBV-IPV administered concomitantly with *OmniHIB*.

Administration: the vaccines were administered by IM injection into the anterolateral thigh.

Solicited signs and symptoms: solicited local symptoms included swelling, pain and redness. Solicited general symptoms included fever.

Follow up of extensive swelling reactions: the reporting of extensive swelling was actively solicited.

Results:

Reports of pain and redness associated with any injection site swelling including swellings not meeting the protocol definition of "large or extensive swelling", and reports of fever in vaccinated subjects

Ninety-six subjects were vaccinated from group 1, 99 vaccinated in group 2. Ninety-four and 99 subjects, respectively, were included in the ATP cohort for the analysis of safety. There was 100% compliance with the return of local symptom sheets. For group 1 there was also 100% compliance for the return of general symptom sheets. For group 2 compliance for general symptom sheets was 99%.

Injection site swelling was reported for 29/94 (30.9%) of subjects (in the ATP cohort) receiving DTPa and for 25/99 (25.3%) of subjects vaccinated with DTPa-HBV-IPV.

Pain was reported for 72/193 (37.8%) DTPa and DTPa-HBV-IPV vaccinees (respectively 40.4% and 35.4% of the groups). Grade 3 pain (cried when limb was moved/spontaneously painful) was reported for 1 DTPa vaccinee.

Redness was reported for 90/193 (46.6%) of DTPa and DTPa-HBV-IPV vaccinees (respectively 42.6% and 50.5%).

Fever (rectal temperature ! 38.0°C) was noted in 31/94 subjects from group 1 (33.0%) and 31/99 subjects from group 2 (31.3%). Grade 3 fever (> 39.5°C, rectal) was reported for 3 subjects from group 2.

Extensive swelling

There was one report of extensive swelling classified as type 2 (diffuse swelling, not involving an adjacent joint) following the administration of DTPa-HBV-IPV. However, for one subject receiving DTPa, subsequent examination of the diary card revealed that a swelling meeting the protocol definition for type 1 had developed.

Onset of the swellings was reported as day 0 or day 1. The recorded duration of extensive swelling was 4 and 5 days, respectively.

No functional impairment was reported.

Both local swellings had a maximum diameter of 90 mm. Redness was reported in both cases, but no induration. Differences in limb circumference (35 mm) was recorded in

association with DTPa-HBV-IPV. The measurement was not available in the second case.

No fever was reported in these subjects.

Both large swelling reactions resolved.

217744/062 (DTPa-HBV-IPV-062) (The Philippines)

Design: an open phase III booster study with two parallel groups. All subjects received DTPa-HBV-IPV/Hib vaccine.

Objectives: the primary objective of the study was to assess the reactogenicity of the study vaccine.

Population: healthy children aged 12 to 15 months who had previously been vaccinated in a three dose primary course with DTPa-HBV-IPV/Hib, either with (group 1), or without (group 2), HBV at birth.

Administration: the vaccine was administered by IM injection into the anterolateral thigh.

Solicited signs and symptoms: solicited local symptoms included swelling, pain and redness. Solicited general symptoms included fever.

Follow up of extensive swelling reactions: the reporting of extensive swelling of the vaccinated limbs was actively solicited.

Results:
(Pooled results from the two groups are summarised here).

Reports of pain and redness associated with any injection site swelling including swellings not meeting the protocol definition of "large or extensive swelling", and reports of fever in vaccinated subjects
Of the 237 subjects vaccinated, 228 were included in the ATP cohort for the analysis of safety. Compliance for the return of symptom sheets was 100%.

Injection site swelling was reported for 89 of the 228 vaccinees (39.0%).

Pain was reported for 109/228 subjects (47.8%). In 12 cases (5.2%) it was scored as grade 3 (cried when limb was moved/spontaneously painful).

Redness was reported in 50.0% of subjects.

Fever (rectal temperature ! 38.0°C, temperature by other routes ! 37.5°C) was observed in 102 subjects (44.7%). In 9 of these (3.9% of the cohort) axillary temperature was recorded as > 39.0°C

Extensive swelling
Extensive swelling reports were completed for 4 subjects (1.7% of the vaccinated cohort). All swellings were reported to be type 1 (local swelling around the injection site, not involving an adjacent joint). Day of onset ranged from day 0 to day 4 and recorded duration of extensive swelling was from 1 to 3 days.

Pain was noted in three of the reports (it was not measured in one subject). One report was of grade 3 pain (cried when limb was moved/spontaneously painful). Moderate functional impairment was also reported in this case. (For the 3 other reports, it was not measured.)

The recorded diameters of the local swellings noted in all four cases ranged from 55 to 90 mm. All cases reported redness and induration. An increase in limb circumference of 20 mm was reported for one case.

Fever was noted for 2 subjects. In neither case did it exceed 38.0°C.

All large swelling reactions resolved.

217744/065 (DTPa-HBV-IPV-065) (Germany)

Design: an open, randomised booster study (phase III), with three parallel groups in a 1:1:1 allocation.

Group1 received DTPa-HBV-IPV/Hib vaccine, co-administered with MMR vaccine (*Priorix*).
Group 2 received DTPa-HBV-IPV/Hib vaccine, co-administered with varicella vaccine (*Varilrix*).
Group 3 received DTPa-HBV-IPV/Hib vaccine alone.

Objectives: the primary objective of the study was to assess the reactogenicity of the study vaccines.

Population: healthy children in their second year of life, previously vaccinated in a primary series with a Pa containing combination vaccine manufactured by GSK Biologicals.

Administration: the DTPa-HBV-IPV/Hib vaccine was administered by IM injection into the anterolateral thigh. Vaccines given concomitantly were administered in the deltoid.

Solicited signs and symptoms: solicited local symptoms included swelling, pain and redness. Solicited general symptoms included fever.

Follow up of extensive swelling reactions: the reporting of extensive swelling of the vaccinated limb was actively solicited.

Results:

Reports of pain and redness associated with any injection site swelling including swellings not meeting the protocol definition of "large or extensive swelling", and reports of fever in vaccinated subjects

A total of 175 subjects were vaccinated. Of these, 173 (from the three groups combined) were included in the ATP cohort for the analysis of safety. Compliance for the return of symptom sheets was 100%.

Swelling at the site of injection of the DTPa-HBV-IPV/Hib vaccine was noted in 59 of the 173 subjects (34.1%).

Pain was reported for 67/173 subjects (38.7%). In seven subjects (4.0%) it was scored as grade 3 (cried when limb was moved/spontaneously painful).

Redness was reported for 87 of the 173 vaccinees (50.3%).

Fever (rectal temperature ! 38.0°C) was observed in 58/114 vaccinees that received vaccines concomitantly (50.9%). A rectal temperature > 39.5°C was recorded in eight (7.0%). For the vaccinees that received DTPa-HBV-IPV alone, the respective figures were 25/59 (42.4%) and 2/59 (3.4%).

Extensive swelling

Extensive swelling reports were completed for five of the 175 subjects in the total cohort (2.9%). All of the reported large swelling reactions followed vaccination with DTPa-HBV-IPV/Hib. Two of the swellings were classified as type 1 (local swelling around the injection site, not involving an adjacent joint), two as type 2 (diffuse swelling, not involving an adjacent joint) and one was not classified. Recorded day of onset ranged from day 1 to day 4 and duration of the extensive swelling ranged from 3 to 6 days.

Pain was reported in three cases and functional impairment in one (for which mild pain was also reported). Neither grade 3 pain nor grade 3 functional impairment were recorded.

Local swellings, ranging in size from 50 to 140 mm were recorded in all cases. Redness was reported in all, induration in three. The measured increase in circumference of the Pa combination inoculated limb compared to the opposite limb ranged from 0 to 20 mm.

Fever (temperature 40.3°C) was reported for one subject (that received Priorix concomitantly).

All large swelling reactions resolved.

217744/066 (DTPa-HBV-IPV-066) (Germany)

Design: an open, randomised booster study (phase III) with two groups in a balanced 1:1 allocation

Group 1 received DTPa-HBV-IPV/Hib vaccine, co-administered with HAV vaccine, *Havrix*, and a second dose of Havrix six months later.
Group 2 received DTPa-HBV-IPV/Hib vaccine alone.

Objectives: the primary objective was to assess the reactogenicity of the study vaccines.

Population: healthy children in the second year of life, previously vaccinated in a primary series with a Pa containing combination vaccine manufactured by GSK Biologicals.

Administration: the DTPa-HBV-IPV/Hib vaccine was administered by IM injection into the anterolateral thigh. Concomitant HAV vaccine (group 1) was administered in the opposite thigh.

Solicited signs and symptoms: solicited local symptoms included swelling, pain and redness. Solicited general symptoms included fever.

Follow up of extensive swelling reactions: the reporting of extensive swelling of the vaccinated limb was actively solicited.

Results:

Reports of pain and redness associated with any injection site swelling including swellings not meeting the protocol definition of "large or extensive swelling", and reports of fever in vaccinated subjects
A total of 82 subjects were vaccinated from the two groups combined. All were included in the ATP cohort for the analysis of safety. There was 100% compliance for the return of symptom sheets.

Injection site swelling was reported at the site of injection of the DTPa-HBV-IPV/Hib vaccine in 32 of the 82 subjects (39.0%).

Pain at the site of injection of the DTPa-HBV-IPV/Hib vaccine was reported in 35/82 vaccinees (42.7%). In 4 cases (4.9%) it was scored as grade 3 (cried when limb was moved/spontaneously painful).

Redness at the site of injection of DTPa-HBV-IPV/Hib was reported for 45/82 of vaccinees (54.8%).

Fever (rectal temperature ! 38.0°C), was observed in 18 of the 41 subjects in group 1 (43.9%) and in 16/41 (39.0%) from group 2. Fever > 39.5°C (rectal temperature) was reported for one subject from group 1 and 5 subjects from group 2.

Extensive swelling
One extensive swelling report was completed. This was for a subject from group 1, at the DTPa-HBV-IPV/Hib injection site. The swelling was categorised as type 2 (diffuse swelling, not involving an adjacent joint). Onset was noted as day one, the duration of extensive swelling was reported to be two days.

Moderate pain and moderate functional impairment were observed.

The diameter of the local swelling was recorded as 80 mm. Redness and induration were also noted. Limb circumferences were not recorded.

There was no fever.

The event resolved.

217744/074 (DTPa-HBV-IPV-074) (Germany)

Design: an open randomised booster study (phase IIIb) with two parallel groups in a 1:1 ratio.

Group 1 received DTPa-HBV-IPV/Hib vaccine
Group 2 received DTPa-IPV/Hib vaccine and concomitant HBV vaccine, *Engerix B*.

Objectives: the primary objective was to assess and compare the incidence of high-grade fever (! 40.0°C) within 4 days after booster vaccination with the study vaccines. One of several secondary objectives was to assess the incidence of large local injection site reactions within 4 days after booster vaccination and causing concern to the vaccinees parents or guardians. A large local injection site reaction was defined in the protocol as a local injection site swelling with one or more of the following: i). diameter > 50mm; ii). noticeable diffuse injection site swelling; iii). noticeable increased circumference of the injected limb. Only swellings meeting these criteria were solicited and recorded in this study, smaller local swellings were not solicited.

Population: healthy children in the second year of life who had previously been primed with licensed vaccines according to the recommendations then in place in Germany.

Administration: vaccines were administered by IM injection into the anterolateral thigh. When HBV vaccine was administered it was given in the opposite thigh.

Follow up of extensive swelling reactions: the reporting of extensive swelling of the vaccinated limb was actively solicited.

Results

A total of 8050 subjects were vaccinated (4032 from group 1 and 4018 from group 2). Swelling, meeting the protocol definition of a large swelling, was reported for 184 of the 7908 vaccinated subjects (3964 in group 1 and 3944 in group 2) that were included in the ATP analysis for safety (2.3%). Three additional swellings meeting the same criteria were observed in vaccinated subjects not included in the ATP analysis.

Thus from the total vaccinated cohort 187/8050 subjects (2.3%) were reported to have developed large injection site reactions.

For group 1 (DTPa-HBV-IPV/Hib) 103 large injection site reactions were reported from 4032 subjects (2.6%). Seventy-three were recorded as large local swellings (70.9% of all large swelling reactions reported for the group and 1.8% of subjects enrolled in the group). Twenty-eight (27.2% of reactions and 0.7% of subjects) were recorded as

diffuse, not involving an adjacent joint and two (1.9% of reactions and 0.05% of subjects) as extensive swelling reactions involving at least one adjacent joint.

For group 2 (DTPa-IPV/Hib + HBV) 72 of the 4018 subjects vaccinated had large swelling reactions at the site of DTPa-IPV/Hib administration (1.8%). [Due to a randomisation failure, one vaccinee from group 2 actually received DTPa-HBV-IPV/Hib vaccine. This subject (for whom a diffuse swelling, not involving an adjacent joint was reported) has been classified as a "DTPa-IPV/Hib" vaccinee for the purposes of this summary.]

There were 50 instances of reports of "large local swellings" following vaccination with DTPa-IPV/Hib (69.4% of the 72 large swelling reports from group 2 and 1.2% of subjects in the group). Nineteen cases (26.4% of swelling reports and 0.4% of subjects in the group) were of diffuse swellings not involving an adjacent joint and three (4.2% of swelling reports and 0.1% of subjects) were recorded as extensive swellings involving at least one adjacent joint.

For all reports combined, the day of onset of the swellings ranged from day 0 to day 3, and the recorded duration of the large swelling from 1 to 14 days. A majority of the reactions had an onset not later than the day after vaccination and in most the duration of the extensive swelling was four days or less.

As noted above, the primary endpoint of the study was the incidence of rectal temperature ! 40°C within four days after vaccination. For the ATP cohort for the analysis of safety, there was no statistically significant difference between the groups with respect to this endpoint: 0.6% of subjects in each group (95% CI 0.4-0.9 for both groups) were recorded as developing fever of this severity. In the ATP cohort for the analysis of safety, there was a statistically significant, but not clinically relevant, increase in the number of subjects having reported fever < 39°C from group 1 as compared to group 2. Fever of any severity (rectal temperature ! 38.0°C, temperature by other routes ! 37.5°C) was recorded in 1479/3964 (37.3%) subjects from group 1 and in 1350/3944 (34.2%) from group 2.

For vaccinees for which large swelling reports were completed, 35.9% (37/103) of the reports from group 1 noted fever (of any severity) and 15.3% (11/72) from group 2. No fever ! 40°C was reported.

671/3964 vaccinees from group 1 demonstrated fever ! 39.5°C (1.7%). For group 2 the respective figure was 64/3944 (1.6%). Of the subjects for whom large swelling reports were completed, there were three cases of fever ! 39.5°C in each group.

Pain was recorded in 55 of the 103 large swelling reports from group 1 (53.3%). In four instances (3.8%) it was graded 3 (cried when limb was moved/spontaneously painful). Functional impairment was noted in 25 instances (24.0% of reports) and graded 3 in two. In 16 cases (15.5%), both pain and functional impairment were reported. Two of the three cases of grade 3 pain also reported impairment: in one of these the degree of functional impairment was also graded 3.

From group 2, pain was noted at the DTPa-IPV/Hib injection site in 37 of the 72 reports (51.4%). In three instances it was graded 3 (4.2%). Functional impairment was noted in 15 reports from this group (19.4%): in two instances it was graded 3. In all of the cases, pain was also reported. The three reports of grade 3 pain also recorded the presence of impairment. In one instance it was graded 3.

The reported diameter of discrete, measurable, local swellings ranged from 30 to 170 mm in group 1 and from 10 to 150 mm in group 2. Redness and induration were reported in 83.4% (146/175) and 70.9% (124/175) of cases, respectively.

Recorded differences in limb circumference ranged from 0 to 60 mm for group 1 and -10 to 60 mm for group 2. (For 47 of the reports from group 1 and 31 of the reports from group 2, circumferences were not measured or not available.)

All the reported injection site reactions resolved.

217744/095 (DTPa-HBV-IPV-095) (Germany)

Design: an open, phase IV booster study with two groups, both of which received DTPa-HBV-IPV/Hib vaccine, *Infanrix hexa*.

One group (referred to below as the "Hexavac" group) had previously been vaccinated with *Hexavac* (Aventis Pasteur).

A second group (described below as the "Infanrix hexa" group) had previously been vaccinated with *Infanrix hexa*.

Objectives: the primary objective of the study was to investigate the immune response to the booster dose. Assessment of the safety and reactogenicity of the study vaccine was one of the secondary objectives.

Population: healthy children aged between 11 and 23 months who had previously been vaccinated in a three dose primary schedule either with *Infanrix hexa* or with *Hexavac*.

Administration: vaccine was administered by IM injection into the anterolateral thigh using a needle of at least one-inch in length.

Solicited signs and symptoms: solicited local symptoms included swelling pain and redness. Solicited general symptoms included fever.

Follow up of extensive swelling reactions: the reporting of large injection site reactions was actively solicited in this study.

Results:

Reports of pain and redness associated with any injection site swelling including swellings not meeting the protocol definition of "large or extensive swelling", and reports of fever in vaccinated subjects

A total of 329 subjects were vaccinated, 163 in the "Hexavac" group and 166 in the "Infanrix hexa" group. The analysis of safety was performed on the total vaccinated

cohort. There was 100% compliance for the return of symptom sheets from the "Hexavac" group and 98.2% from the "Infanrix hexa" group. (Three-hundred-and-twenty-four subjects were eligible to be included in the ATP cohort for the analysis of safety, respectively 160 in the "Hexavac" group and 164 in the "Infanrix hexa" group".)

Injection site swelling was reported for 28.8 % of vaccinees (47/163) in the "Hexavac" group. In the "Infanrix hexa" group swelling was reported for 40.4% (67/166).

Pain was recorded from the "Hexavac" group in 44 instances (27.0% of the vaccinated cohort) and in 65 instances from the "Infanrix hexa" group (39.2%). There was one report of grade 3 pain (cried when the limb was moved/spontaneously painful) in the "Hexavac" group (0.6%) and six reports of grade 3 pain in the "Infanrix hexa" group (3.6%).

Redness was noted for 64/163 subjects in the "Hexavac" group (39.3%) and for 96/166 subjects (57.8%) in the "Infanrix hexa" group.

Fever (rectal temperature ! 38.0°C) was noted for 57 subjects in the "Hexavac" group (35.0%) and 52 subjects in the "Infanrix hexa" group (31.3%). Grade 3 fever (rectal temperature > 39.5°C) was reported for five subjects (3.0%) in the first group and for four vaccinees (2.4%) in the second.

Extensive swelling
Large injection site reactions were reported for four subjects, all in the "Infanrix hexa" group. Three were characterised as local, not involving an adjacent joint and one as diffuse, not involving an adjacent joint. Time of onset was recorded as day 0 or day 1. Reported duration of the extensive swelling ranged from 2 to 8 days.

Pain was recorded in three instances: in two it was graded 3. Functional impairment was not observed.

The diameter of discrete local swellings ranged from 50-100 mm. Redness and induration were respectively noted in three and two reports.

Increase in circumference of the vaccinated versus the opposite limb was either not measured, or not recorded.

Fever was noted for two subjects. (The rectal temperature was 38.1 °C in both cases).

All large swelling reactions resolved.

455697/001 (DTPa-HAV-IPV-001) (Lithuania)

Design: a randomised, open phase II booster study with three parallel groups in a balanced (1:1:1) allocation.

Group I received an experimental DTPa-HAV-IPV vaccine mixed with an experimental Hib MenC combination vaccine and a second dose of HAV 6 months later.

Group 2 received the experimental DTPa-HAV-IPV vaccine mixed with Hib vaccine and a second dose of HAV 6 months later.
Group 3 received DTPa-IPV/Hib given concomitantly with HAV and a second dose of HAV 6 months later.

Only the results for group 3 are considered here.

Objectives: the primary objective of the study was to assess the reactogenicity of the study vaccines in terms of grade 3 local or general, solicited or unsolicited symptoms occurring within 8 days after vaccination, including any occurrence of grade 3 swelling.

Population: healthy children aged 17 to 20 months who had previously received three doses of DTPa-IPV/Hib at 3, 4.5 and 6 months of age.

Administration: vaccine was administered by IM injection into the thigh.

Solicited signs and symptoms: solicited local symptoms included swelling, pain and redness. Solicited general symptoms included fever.

Follow up of extensive swelling reactions: extensive swelling of the vaccinated limb was actively solicited.

Results:

Reports of pain and redness associated with any injection site swelling including swellings not meeting the protocol definition of "large or extensive swelling", and reports of fever in vaccinated subjects
A total of 163 subjects were vaccinated from group 3. Of these, 161 were eligible to be included in the ATP cohort for the analysis of safety. Compliance for the return of symptom sheets was 100%.

There were 72 reports of swelling at the site of injection of DTPa-IPV/Hib for the 161 subjects in group that were included in the ATP cohort for the analysis of safety (44.7%)

Pain at the site of injection of DTPa-IPV/Hib was reported for 94/161 (58.4%). There were 12 reports of grade 3 pain (cried when limb was moved/spontaneously painful - prevented normal activity) (7.5% of the cohort).

Redness was reported for 95 subjects (59.0%).

Fever (oral/axillary temperature ! 37.5°C) was noted for 63/161 subjects (39.1%). Five subjects (3.1%) demonstrated fever > 39°C.

An increase in limb circumference after the administration of DTPa-IPV/Hib of > 25 mm was recorded in the diary cards for 7 subjects (4.3%). For two subjects an increase of > 50 mm was noted. (There was one report of an increase of the same order after HAV).

Extensive swelling
Parents/guardians of 14 of the subjects from group 3 contacted the investigator. For two of the subjects it was not possible to establish which vaccine (DTPa-IPV/Hib or HAV)

had been administered. One event followed vaccination with HAV. Of the 11 reactions (6.7% of the vaccinated cohort) that were known to have followed vaccination with DTPa-IPV/Hib, five were noted as type 1 (local swelling around the injection site, not involving an adjacent joint) , one as type 2 (diffuse swelling not involving an adjacent joint) and for five the type was not specified.

The reported time of onset ranged from 1 to 2 days, and duration of the extensive swelling was recorded as being from 1 to 5 days.

Pain was noted in 10/11 reports. There were no reports of severe pain and no reports of functional impairment.

The diameter of the swellings noted in the reports ranged from 12-120 mm, and the increase in limb circumference from 0-40 mm. Redness was noted in 10/11 instances and induration in three.

Fever was recorded for two subjects (the axillary temperature in both cases was 37.6°C).

All large swelling reactions resolved.

711202/008 (MenC-TT-008) (Germany)

Design: an open, non-randomised booster study with five groups. All subjects received one fifth of a dose of meningococcal vaccine (*Mencevax ACWY*) (plain polysaccharide) and a concomitant dose of DTPa-HBV-IPV/Hib.

Objectives: the primary objective was to evaluate immune memory following a *primary* vaccination course of meningococcal serogroup C vaccine. Evaluation of the safety and reactogenicity of the concomitant administration of meningococcal polysaccharide and DTPa-HBV-IPV/Hib as a booster dose was a secondary objective.

Population: healthy children aged 12 to 15 months. Two of the groups had received primary vaccination with experimental meningococcal serogroup C conjugate/Haemophilus influenzae type-b vaccines, one group had received experimental meningococcal serogroup C vaccine and one *Meningitec* (Wyeth). (All administered in a 3, 4 and 5 months schedule). The last (5th) group had not previously been vaccinated with meningococcal serogroup C vaccine. The first four groups had also received a full, three-dose primary vaccination course with DTPa-HBV-IPV/Hib or DTPa-HBV-IPV. The last group had received routine paediatric primary vaccination according to current recommendations in Germany.

Administration: the vaccines were administered by IM injection into opposite anterolateral thighs.

Solicited signs and symptoms: solicited local symptoms included swelling pain and redness. Solicited general symptoms included fever.

Follow up of extensive swelling reactions: the reporting of large injection site reactions was actively solicited in this study.

Document 1

CONFIDENTIAL

Results:

Reports of pain and redness associated with any injection site swelling including swellings not meeting the protocol definition of "large or extensive swelling", and reports of fever in vaccinated subjects

A total of 459 subjects were enrolled into the study and vaccinated. Of these, 448 were eligible to be included in the ATP cohort for the analysis of safety. The primary analysis of safety was conducted on the total vaccinated cohort. Compliance for the return of symptom sheets was ! 97.6%.

Injection site swelling at the site of injection of DTPa-HBV-IPV/Hib was reported for 113 vaccinees (24.6% of the total cohort)

Pain was reported for 97 subjects (21.1%). There were three reports of grade 3 pain (cried when limb was moved/spontaneously painful) (0.7%).

Redness was reported for 164 subjects (35.7%).

Fever (rectal temperature ! 38.0°C) was noted in 103 subjects (22.4%). A temperature > 39.5°C was recorded in three vaccinees (0.7%).

Extensive swelling

Extensive swelling reports were submitted for six subjects. All reports related to the site of injection of DTPa-HBV-IPV/Hib. Only two of the reports (0.4% of the vaccinated cohort) met the pre-established definition of extensive swelling: the other four were reports of local swelling of 50 mm diameter or less. Both of the events that met the definition were local swellings, not involving an adjacent joint.

In both cases day of onset was day 2. Recorded duration was five and three days.

There was no pain associated with either event. Mild functional impairment was noted for one.

Diameter of the swellings was 80 mm and 110 mm. One swelling was accompanied by redness and induration. The other case was accompanied by fever (rectal temperature 38.1°C).

Both events resolved.

With respect to the swellings that did not correspond to the pre-established definition, one report recorded mild pain, and one moderate. All were accompanied by redness. There was no functional impairment. No fever was reported.

These events were reported to have resolved within one to four days.

404286/006 (DTPa-HBV-IPV/Hib-MenC [Hepta]-006) (Germany)

Design: an open, randomised, controlled phase II booster study with four groups.

Three of the groups received DTPa-HBV-IPV/Hib vaccine, one group received an experimental DTPa-HBV-IPV/Haemophilus influenzae type b and meningoccocal C polysaccharide combination vaccine. The results for the last group are not considered here. Two of the three groups included in the summary received 1/5th of a dose of Mencevax AC, concomitantly. One group received only DTPa-HBV-IPV/Hib

Objectives: the primary objective of the study was to evaluate immune memory induced by primary vaccination. (For primary vaccination, depending upon group assignment, subjects had received either one of three developmental DTPa-HBV-IPV/Haemophilus influenzae type b and meningoccocal C polysaccharide combination vaccines or DTPa-HBV-IPV/Hib.) Evaluation of safety and reactogenicity was one of several secondary objectives.

Population: healthy children aged 12 to 24 months who had previously received a Pa based combination vaccine, either commercial or experimental, for primary vaccination.

Administration: vaccines were administered by IM injection in the thigh. When two vaccines were administered they were injected into opposite thighs.

Solicited signs and symptoms: solicited local symptoms included swelling pain and redness. Solicited general symptoms included fever.

Follow up of extensive swelling reactions: the reporting of large injection site reactions was actively solicited in this study. The characteristics of what were to be considered to be large local injection site reactions (swelling with longest diameter > 50 mm, noticeable diffuse swelling, noticeable increase in limb circumference) were defined in the protocol. Such swellings were to be examined by the investigator. Swellings were to be categorised by the investigator, following the physical examination, into one of three categories: (i). local swelling around the injection site, not involving adjacent joints; (ii). diffuse swelling, not involving adjacent joints; (iii). swelling involving at least one adjacent joint. Using a specific form in the CRF, the diameter of any local swelling (if measurable, i.e. circumscribed) was to be noted, as was the diameter of any associated redness or induration. (It was anticipated that in some cases a discrete local swelling might be superimposed on a diffuse swelling.) Also, the circumference of the vaccinated limb, and that of the opposite limb, was to be measured, and any difference recorded.

The timing of onset, duration and outcome of the event were to be noted, and pain and functional impairment, if present, scored for severity. Temperature was to be recorded.

Results:

Reports of pain and redness associated with any injection site swelling including swellings not meeting the protocol definition of "large or extensive swelling", and reports of fever in vaccinated subjects

A total of 191 subjects were enrolled and received a booster dose of DTPa-HBV-IPV/Hib. Forty-six children received DTPa-HBV-IPV/Hib alone, 145 received DTPa-HBV-IPV/Hib and 1/5th of a dose of Mencevax AC concomitantly. The principal analysis of safety was performed on the vaccinated cohort. (176 children were eligible

for inclusion in the ATP cohort for the analysis of safety.) There was 100% compliance for the return of symptom sheets.

Injection site swelling at the site of injection of DTPa-HBV-IPV/Hib was reported for 239.% of the children who received the vaccine alone. Pain was reported for 12.6% and redness for 34.8%. (The analysis of reactogenicity was performed using sites sites together for the group which received DTPa-HBV-IPV/Hib and Mencevax AC).

Fever, (rectal temperature ! 38.0°C) was reported for 69/145 of the vaccinees receiving concomitant vaccination (47.6%). There were 26 reports of fever from the 46 children in the group receiving DTPa-HBV-IPV/Hib alone (56.5%). Fever > 39.0°C was reported for 15 subjects and seven subjects, respectively (10.3% and 15.2%). There was one report of fever > 40.0°C: this was for a vaccinee receiving concomitant vaccination.

Extensive swelling
Extensive swelling reports were completed for six subjects (3.1% of subjects vaccinated). Two of these recorded local swellings (diameter of 50mm) that did not meet the definition of an extensive swelling. All swellings were at the site of injection of the DTPa-HBV-IPV/Hib vaccine. Three of the four swellings that met the protocol definition of "extensive" were local, one was diffuse, not involving an adjacent joint.

Day of onset was day one or day two except for one report for which it was day five. Duration of the event ranged from three to nine days.

Mild or moderate pain was noted in three of the four reports. Mild or moderate functional impairment was recorded in two (both also noted pain).

Local swellings ranged in diameter from 82 mm to 230 mm. Redness was recorded in all, induration in one. Measured increase in limb circumference for the two reports in which it was recorded was 40 mm and (for the diffuse swelling) 80 mm.

Fever was reported for two of the four subjects. None of the four reports described fever > 39.0°C. One of the reports of swelling that did not meet the protocol definition noted fever of 39.9°C (rectal).

All large swelling reactions resolved.

Narrative description of study: booster vaccination at 4 to 6 years in children previously vaccinated at 3,5 and 11-12 months with Pa containing combination vaccine.

213503/045 (DTPa-IPV-045) (Italy and Sweden)

Design: an open, randomised, phase IIb booster study with two parallel groups in a balanced 1:1 allocation.

Group 1 received DTPa-IPV vaccine.
Group 2 received DTPa vaccine with IPV vaccine, (*Imovax-Polio*, Aventis MSD), given concomitantly.

Document 1

CONFIDENTIAL

Objectives: the primary objective was to demonstrate that the DTPa-IPV vaccine was at least equivalent to the DTPa + IPV vaccines administered separately, in terms of immunogenicity to all vaccine antigens one month after vaccination at 4-6 years of age. Assessment of the safety and reactogenicity of the study vaccines was a secondary objective.

Population: healthy children between and including 4 to 6 years of age who had previously been vaccinated with three doses of DTPa and IPV or OPV vaccines at 3, 5 and 11 to 12 months of age. (An additional dose of OPV was given to Italian subjects at 3 years of age).

Administration: the vaccines were administered by deep IM injection into the deltoid using a needle of at least one-inch in length. The concomitantly administered vaccines were injected in opposite limbs.

Solicited signs and symptoms: solicited local symptoms included swelling, pain and redness. Solicited general symptoms included fever.

Follow up of extensive swelling reactions: reporting of large injection site swellings was actively solicited. However, due to an error, a reminder for the parents/guardians to contact the investigator if a large swelling reaction occurred was omitted from the diary card.

Results:

Reports of pain and redness associated with any injection site swelling including swellings not meeting the protocol definition of "large or extensive swelling", and reports of fever in vaccinated subjects

A total of 211 subjects were vaccinated from group 1 and 205 from group 2. Of these, 210 and 203, respectively, were eligible to be included in the ATP cohort for the analysis of safety. The analysis of safety was performed on the total vaccinated cohort. Compliance with the return of symptom sheets was ≥ 98.0%.

Injection site swelling was reported for 112 of the 211 subjects from group 1 (53.1%). From group 2, injection site swelling (at the DTPa injection site) was reported for 106 of the 205 subjects (51.7%).

Pain was reported for 150/211 subjects from group 1 (71.1%) and 132/205 (at the site of injection of DTPa) from group 2 (64.4%). Grade 3 pain (cried when limb was moved/spontaneously painful) was noted for 6 subjects in group 1 (2.8%) and 9 subjects (4.4%) from group 2.

Fever (rectal temperature ≥ 38.0°C, temperature by other routes ≥ 37.5°C) was reported for 44/211 (20.9%) of subjects from group 1 and 34/205 (16.6%) from group 2. A rectal temperature > 39.5°C was reported for one subject from group 1 and 3 subjects from group 2.

Extensive swelling

The parents/guardians of 11 subjects contacted the investigator to report a large injection site swelling. However, an additional 52 cases with injection site swelling with a diameter > 50 mm were identified by the sponsor via the diary cards, prior to data analysis.. Consequently, enquiries were initiated in order to obtain additional information from the parents/guardians. Extensive swelling forms were completed *post-hoc* by study nurses or parents/guardians using information from the diary cards and from memory. As a result, measurements of the diameter of swellings and of associated pain, redness, and measured differences in limb circumference are missing in many cases. Only a few measurements of induration are available. The presence/absence of fever was not investigated – or not recorded – in 29/63 subjects.

In total 28 large swelling reactions were noted following vaccination with DTPa-IPV (13.2% of the 211 subjects in the vaccinated cohort from group 1). Thirty-five large swelling reactions were noted after vaccination with DTPa (17.1% of the 205 vaccinated subjects from group 2).

For 21/28 (75.0%) of the subjects for whom large swelling was reported from group 1 the swellings were defined as large local reactions. For seven subjects in this group (25.0% of swelling reports) they were recorded as diffuse, not involving an adjacent joint.

For group 2, 27/35 reports noted large local reactions (77.1%). Five of 35 reactions (14.3%) were recorded as diffuse and 3/35 reported to involve at least one adjacent joint (8.6%).

For all reports combined the day of onset ranged from 0-7 and duration of extensive swelling was reported to range from 1-57 days (excluding the one subject for which 57 days was reported, the duration ranged from 1-15 days).

Severe pain was reported for one subject from group 2. It was associated with a diffuse reaction. There was only one report of severe functional impairment. This was also from group 2, and associated with a large local reaction. It was noted that in this last case there was no associated pain.

Swelling diameter was measured and recorded for a total of 34/63 subjects. It ranged from 60-192 mm for group 1 and 60-200 mm for group 2. The presence of redness was noted in all reports were swelling diameter was recorded

In the majority of instances the circumference of the limbs was not measured or not recorded.

Among the 33 subjects for whom a record of temperature is available, there were seven reports of fever (three from group 1 and four from group 2): all of these were of fever " 38.5°C.

All of the large swelling reactions resolved.

Document 1

CONFIDENTIAL

Narrative descriptions of studies: booster vaccination at 4 to 6 years in children who had previously received 4 doses of Pa containing combination vaccine.

208355/118 (APV-118) (Germany)

Design: a randomised, single blind, comparative booster study with three groups in a 2:1:1 ratio.

One group received GSK Biologicals reduced antigen content dTpa vaccine (*Boostrix*).
One group received DTPa vaccine.
One group received commercial Td vaccine (*Td-pur*, Chiron-Behring) followed at least one month later by either an experimental pa vaccine or by licenced Pa vaccine (*Pac Mérieux*). The Pa/pa dose is not addressed in this narrative.

Objectives: the primary objective of the study was to assess and compare the immune response following a booster dose of dTpa and DTPa vaccines. Comparison of the reactogenicity of the study vaccines was one of the secondary objectives.

Population: healthy children aged 4 to 6 years, previously vaccinated with four doses of DTPa vaccine in the first two years of life.

Administration: vaccines were administered by intramuscular injection in the deltoid region.

Solicited signs and symptoms: solicited local symptoms included swelling, pain and redness. Solicited general symptoms included fever.

Follow up of extensive swelling reactions: parents/guardians were instructed to contact the investigator immediately if the subjects manifested any signs or symptoms that raised their concern. Parents spontaneously contacting the investigator to report extensive local swelling were asked to present the child for an examination. The investigator was to document the characteristics of the swelling, and the temperature of the subject, on a specific form in the CRF.

The date of onset and the date of resolution were to be recorded. The intensity (level of discomfort/interference with normal activities) was to be assessed.

The circumferences of the injected and opposite limbs were to be recorded.

The presence or absence of pain, redness and warmth were to be noted, and if any of these were present, a distinction made between localised and diffuse reactions.

Results:

Reports of pain and redness associated any with injection site swelling including swellings not meeting the protocol definition of "large or extensive swelling", and reports of fever in vaccinated subjects

A total of 422 subjects were vaccinated in this study, 211 in the dTpa group, 107 in the DTPa group and 104 in the group that received Td. Sixty-five subjects were not included in the ATP cohort for the analysis of safety. In the majority of instances the reason for elimination was that the previous vaccination history was not in compliance with the protocol. Compliance for the return of symptom sheets in the ATP cohort was 100%.

Injection site swelling was reported for 58/180 of the dTpa recipients (32.2%), 39/90 of the DTPa recipients (43.3%) and 30/87 of the Td recipients (34.5%) included in the ATP cohort for the analysis of safety. Swelling ! 50 mm in diameter was recorded for 24 subjects from the first group (13.3%), 14 subjects from the second (15.6%) and 12 from the third (13.8%).

Pain was reported for 86/180 dTpa recipients (47.8%), 57/90 DTPa recipients (63.3%) and 45/87 Td recipients (51.7%). Grade 3 pain (preventing normal daily activity and needing medical advice) was reported for 2 subjects from each group (1.1%, 2.2% and 2.3%, respectively).

Redness was recorded for 61/180 (33.9%) of subjects receiving dTpa, 44/90 (48.9%) of DTPa vaccinees and 32/87 (36.8%) of Td vaccinees.

Fever (rectal temperature ! 38.0°C, temperature by other routes ! 37.5°C) was recorded (as were other symptoms) over 15 days in this study. For fever with onset within three days of vaccination there were 17 reports following vaccination with dTpa (9.4% of the group), 11 reports following DTPa (12.2%) and 11 reports following the administration of Td (12.6%). Over the total observation period the respective figures were 36/180 (20.0%), 20/90 (22.2%) and 28/87 (32.2%).

Grade 3 fever (rectal temperature ! 39.6°C, temperature by other routes ! 39.1°C) was reported for 10 subjects (5.6%) from the first group, 4 subjects (4.4%) from the second and 4 subjects (4.6%) from the third.

Extensive swelling

The parents of 22 subjects spontaneously contacted the investigator to report swelling. Eight reports followed the administration of dTpa (3.8% of the vaccinated cohort receiving dTpa); nine followed DTPa (8.4% of all DTPa recipients) and five followed Td (4.8% of all Td vaccinees). For one subject in the DTPa group, extensive swelling had also been reported after the fourth dose.

In two cases, both of which followed the administration of DTPa, the swelling was recorded as extending from elbow to shoulder. In one instance, also following DTPa, the swelling was noted to include the chest.

The reported day of onset of the reactions ranged from 0 to 2 days with one exception: for one subject vaccinated with Td, swelling was noted to have occurred 32 days after vaccination. The recorded duration of the events ranged from two to five days, except for one report following vaccination with Td for which the duration was recorded as seven days.

In the dTpa group, six of the eight reports noted pain and seven, warmth. For the DTPa group all reports recorded pain and warmth. Two of the five reports following Td noted pain and all recorded warmth. All reports recorded some level of discomfort. In all except three instances - one following dTpa and two following DTPa, in which the level of discomfort was graded 3 (severe) - the intensity was graded mild or moderate.

Approximately two-thirds of reports of redness, swelling and pain from each group were classed as local (rather than diffuse).

The diameter of local swellings ranged from 10 to 200 mm for the events that followed vaccination with dTpa, 22 to 250 mm after DTPa and 65 to 280 mm after Td. Redness was noted in all except one of the 22 reports.

The measured increase in circumference of the vaccinated limb ranged from 15-60 mm for the cases that followed dTpa, 20-70 mm after DTPa and 15-43 mm following Td.

Fever was reported in one instance following dTpa, and in one case after DTPa. No grade 3 fever was reported.

All large swelling reactions resolved.

208355/120 (APV-120) (Germany)

Design: an open, uncontrolled, non-randomised phase III booster study with all subjects receiving DTPa vaccine.

Objectives: the primary objective of the study was to evaluate the reactogenicity of the vaccine.

Population: healthy children of between 4 and 6 years of age, previously vaccinated with four doses of DTPa vaccine in the first two years of life.

Administration: vaccine was administered by deep IM injection into the deltoid muscle.

Solicited signs and symptoms: solicited local symptoms included swelling, pain and redness. Solicited general symptoms included fever.

Follow up of extensive swelling reactions: parents/guardians were instructed to contact the investigator immediately if the subjects manifested any signs or symptoms that raised their concern. Parents spontaneously contacting the investigator to report extensive local swelling were asked to present the child for an examination. The investigator was to document the characteristics of the swelling, and the temperature of the subject, on a specific form in the CRF.

The date was onset and the date of resolution was to be recorded. The intensity (level of discomfort/interference with normal activities) was to be scored.

The circumferences of the injected and opposite limbs were to be recorded.

Doc ID:REGU_200504_83 1.1

The presence or absence of pain, redness and warmth were to be noted and, if any of these were present, a distinction made between localised and diffuse reactions.

Results:

Reports of pain and redness associated with any injection site swelling including swellings not meeting the protocol definition of "large or extensive swelling", and reports of fever in vaccinated subjects

A total of 413 subjects were vaccinated. Thirty-four subjects were eliminated from the ATP cohort for the analysis of safety. In the majority of instances subjects were eliminated due to the vaccine having been administered at the wrong site. Thus for 379 of the doses administered recipients were eligible to be included in the ATP analysis. Compliance for the return of symptom sheets in the ATP cohort was 99.2%.

Injection site swelling was reported for 194 of the 379 subjects (51.2%). In 80 instances (21.1%) the diameter of the swelling was recorded as ! 50 mm.

Pain was noted for 192/379 subjects (50.7%). In six instances the event was graded 3 (an adverse event which prevented normal everyday activities and needed medical advice).

There were 197 reports of redness (52.0%).

Fever (rectal temperature ! 38.0°C, temperature by other routes ! 37.5°C) was recorded for 15 days in this study (as were other symptoms). There were 40 reports of fever with onset within three days of vaccination (10.6%). Over the total observation period there were 94 reports (24.8%). Grade 3 fever (rectal temperature ! 39.6°C, temperature by other routes ! 39.1°C) was recorded for nine subjects (2.4%).

Extensive swelling

The parents of 26 subjects (or 6.3% of the cohort) spontaneously contacted the investigator to report swelling. (All of the reports involved subjects that had been vaccinated according to protocol.)

Two (0.5%) of the swellings were regarded as notable by the investigator. One was described as a strong swelling of the upper arm from shoulder to elbow and one as swelling of the whole upper arm, including the shoulder with the appearance of an "empty hot-water bottle". There was no fever, or impairment of general condition, in either case.

All of the swellings had an onset within three days. Duration of the events was recorded to have ranged from one to 10 days.

Pain was noted in 23/26 instances (88.5%). One swelling was graded 3 in intensity.

The recorded diameter of local swellings ranged from 0-250 mm. Redness was noted in all cases and warmth in 23/26.

Approximately three-quarters of reports of pain were classified as diffuse. Rather more than half of reports of redness and warmth were also classified as diffuse.

The increase in circumference of the vaccinated arm ranged from 12-160 mm.

Fever was reported in three of the 26 vaccinees (11.5%). There were no reports of grade 3 fever.

All large swelling reactions resolved.

213503/046 (DTPa-IPV-046) (Australia)

Design: an open, randomised phase IIIb booster study with two groups in a 1:1 assignment.

> Group 1 received DTPa-IPV vaccine concomitantly with MMR vaccine (*Priorix*).
> Group 2 received DTPa vaccine concomitantly with IPV (*IPOL*: Aventis Pasteur) and MMR vaccine (*Priorix*).

Objectives: the primary objective of the study was to demonstrate that the immunogenicity of the DTPa-IPV vaccine was at least as good as that of DTPa and IPV administered separately, when both groups received a concomitant injection of MMR vaccine. Assessment of the safety and reactogenicity of the study vaccines was a secondary objective.

Population: healthy children aged 4 to 6 years who had previously received 4 doses of a Pa based combination vaccine.

Administration: the DTPa and DTPa-IPV vaccines were administered by deep IM injection into the deltoid region. IPV and MMR vaccines were administered by subcutaneous injection into the deltoid region.

Solicited signs and symptoms: solicited local symptoms included swelling, pain and redness. Solicited general symptoms included fever.

Follow up of extensive swelling reactions: reporting of large swelling reactions was actively solicited.

Results:

Reports of pain and redness associated with any injection site swelling including swellings not meeting the protocol definition of "large or extensive swelling", and reports of fever in vaccinated subjects

A total of 362 subjects were vaccinated, 181 in each group. Of these subjects 338 (171 from group 1 and 167 from group 2) were included in the ATP cohort for the analysis of safety. (For the majority of the subjects the reason for elimination was that they had previously received vaccines not foreseen by the protocol). Compliance with the return of symptom sheets was ! 99.4%.

There were 103 reports of swelling at the site of injection of DTPa-IPV for the 171 subjects from the ATP cohort in group 1(60.2%). Of these, 41 were reported to have a diameter > 50 mm ((24.0% of subjects in the group).

Also from the ATP cohort, 109/167 swellings were noted after vaccination with DTPa (65.3%). Of these, 47 (28.1%) were > 50 mm in diameter.

Pain at the injection site of the DTPa-IPV vaccine was reported for 137 subjects (80.1%). In 12 subjects (7.0%) it was recorded as grade 3 (cried when limb was moved/spontaneously painful).

There were 107 reports of pain at the site of injection of DTPa (64.1%). Grade 3 pain was recorded for six of these subjects (3.6%).

Redness was reported for 80.7% of DTPa-IPV recipients and for 77.2% of subjects receiving DTPa.

Fever ! 37.5°C (measured by the axillary route during a 15 day follow up period) was reported for 39 subjects receiving DTPa-IPV and MMR (22.8%). Three subjects in this group (1.8%) demonstrated fever > 39.0°C. For the group receiving DTPa + IPV + MMR there were 45 reports of fever (26.9%) and one of fever > 39.0°C (0.6%).

Extensive swelling
All reported large injection site swellings occurred at the site of injection either of DTPa-IPV or of DTPa.

A total of 43 extensive swelling reports were completed for subjects who received DTPa-IPV. Forty-two of these related to the 171 vaccinees that were included in the ATP cohort for the analysis of safety. One report followed swelling in a subject in group I who was eliminated from the ATP analysis because of an unknown previous vaccination history. Thus large swelling reports were completed for 23.8% of the total vaccinated cohort that received DTPa-IPV.

Thirty-two of the 43 reports were of local swelling > 50 mm in diameter (74.4% of reports. One swelling was recorded as diffuse (2.3%) and 10 were reported to involve an adjacent joint (the shoulder joint) (23.3%).

Forty-nine large swelling reports were completed following vaccination with DTPa. (27.1% of the total vaccinated cohort from group 2). (All reports involved subjects included in the ATP cohort). Thirty of the reports were of local swelling > 50 mm in diameter (61.2% of reports). Nine reports (18.4%) were of diffuse swelling not involving an adjacent joint and 10 (20.4%) documented a swelling that involved the shoulder joint.

In four instances in the DTPa-IPV group (2.2% of the vaccinated cohort) swelling was reported to extend beyond the shoulder and in two (1.1%) upper arm swelling was recorded. In the DTPa group swellings extending beyond the shoulder were recorded for 2 subjects (1.1% of the vaccinated cohort). Upper arm swelling was also noted for two subjects.

For all reports combined the recorded day of onset ranged from 0-3 days with all except one event starting within 2 days. Duration of extensive swelling was reported to be from 1-18 days, with most reactions being recorded as having resolved within four days.

Document 1

CONFIDENTIAL

For the DTPa-IPV group, 27/43 reports (62.8%) recorded pain. For DTPa vaccinees pain was noted in 27/49 reports (55.0%). In four instances, all in the group receiving DTPa-IPV, it was recorded as grade 3. Functional impairment was reported for a total of 28 subjects (14 in each group). In two events it was graded 3. Both of these cases were in the DTPa-IPV group and in both grade 3 pain was also noted.

The diameter of discrete, measurable local swellings ranged from 40-170 mm in the DTPa-IPV group and 40-210 mm in vaccinees receiving DTPa. Redness was noted for most subjects, induration for less than half.

Recorded differences in limb circumference ranged from 0-62 mm in the DTPa-IPV group and 5-85 mm in subjects receiving DTPa.

Fever was noted in seven DTPa-IPV vaccinees and in two DTPa vaccinees. There were no reports of fever > 39.0°C in any of the vaccinees for whom extensive swelling reports were completed.

All large swelling reactions resolved.

2.7.4.1.2 Overall Extent of Exposure

For the 18 clinical studies combined, a total of 13604 subjects received a vaccine from the *Infanrix* range. In 12306 instances the dose administered was a first booster dose during the first year of life that followed three doses of a Pa containing combination vaccine during the first six months of life. Four hundred and sixteen vaccinees received a booster dose at between 4 and 6 years of age following vaccination with a Pa containing combination vaccine at 3, 5 and 11 to 12 months of age. A further 882 children received a second booster dose at between 4 and 6 years; all children had been primed (in the first 6 months of life) and boosted between 12 and 24 months, with a Pa based vaccine.

An overview of the vaccines of the *Infanrix* range that were administered, by vaccine, study, dose and age is provided in table 2.

2.7.4.1.3 Demographic and Other Characteristics of Study Population

The key characteristics of the populations studied (age and prior vaccination history) are also summarised in table 2.

Subjects in all studies were to be determined to be free of obvious health problems as established by medical history and clinical examination prior to inclusion in the study. Exclusion criteria included, but were not limited to, a history of allergic disease or reactions likely to be exacerbated by any component of the vaccine.

1.7.4.2 Adverse Events

1.7.4.2.1 Analysis of Adverse Events

Safety and Reactogenicity Reporting in All Studies

Local and general signs and symptoms following vaccination were actively solicited in all of the studies. Solicited signs and symptoms were to be recorded by parents or guardians for a period of time that varied from study to study, depending upon the specific requirements developed in the protocol but was invariably at least four days (the day of vaccination and three subsequent days). Diary cards were used for this purpose. In all studies except one, reports of any swelling reactions (irrespective of size or nature) were solicited. In study 217744/074 only swellings meeting the pre-established criteria for large or extensive swellings were solicited. The diary cards also allowed for the recording of unsolicited signs and symptoms after the end of the period of active solicitation. Unsolicited signs and symptoms were generally to be recorded over a period of one month. Solicited signs and symptoms noted subsequently to the period of active follow-up were recorded as unsolicited signs or symptoms.

In addition to swelling, solicited signs and symptoms included (but were not limited to) redness and pain at the injection site and fever. The greatest diameter of any redness or swelling was to be recorded. Solicited signs and symptoms were graded for intensity by the sponsor, prior to analysis, according to criteria defined in the protocol. Pain was

graded on a scale from 0 to 3. It was graded 3 when the vaccinee cried when the limb was moved or the area was spontaneously painful.

Local solicited adverse events occurring in temporal relationship to vaccination were considered causally related to vaccination. When large swelling reactions were reported, investigators were required to note whether there could have been any other apparent explanation for the swelling.

Statistical analyses were descriptive.

No clinical laboratory investigations were planned as part of the analysis of safety.

All study protocols required that serious adverse events (SAEs) be reported to the sponsor within 24 hours regardless of the eventual causal relationship to the study vaccine or vaccines.

In studies 208108/076, 213503/045, 213503/049, 217744/066, 217744/095, 404286/006 and 711202/008, the principal analysis of solicited local and general signs and symptoms was based upon the total vaccinated cohort. For all of the other studies this analysis was based upon the "according to protocol" (ATP) cohort for the analysis of safety. Reasons for exclusion from the ATP cohort were documented in all studies. With the exception of four studies (208355/118, 208355/120, 213503/046 and 404286/006) less than 5.0% of subjects were excluded from the ATP analysis (table 3). Reasons for exclusion from the analysis of individual subjects were documented in the study reports. Principal reasons for exclusion were a prior vaccination history that was not in accordance with the requirements of the protocol, the administration of vaccine forbidden by the protocol or randomisation failure.

Table 3 Study cohorts by dose and study – vaccinees receiving an Infanrix range vaccine

Type of study	Study	Vaccinated	ATP analysis of safety	Principal analysis of safety
1st booster in the in the 2nd year of life after a 3 doses of Pa containing vaccine in the first six months of life	058	1149	1138	1138
	059	443	440	440
	061	195	193	193
	062	237	228	228
	065	175	173	173
	066	82	82	82
	074	8050	7908	7908
	095	329	324	329
	043	200	199	199
	049	344	341	344
	001	163	161	161
	076	288	288	288
	008	459	448	459
	006	191	176	191
1st booster at 4-6 years of age after Pa vaccine at 3, 5, 11/12 months	045	416	413	416
2nd booster dose at 4-6 years after Pa priming and booster in the first two years of life	046	362	338	338
	118	107	90	90
	120	413	379	379

The denominator that has been used to calculate the incidence of large or extensive swelling reactions in this summary, for all studies, is the total vaccinated cohort.

Compliance with reporting requirements (return of symptom sheets) was analysed in all studies. There was a high level of compliance for the return of symptom sheets in all of the studies (! 95.0% in all and ! 98.0% in most).

Fever and severe (grade3) fever: for cultural and other reasons the temperature was not always measured in the same way. In general, it was taken either by the rectal or the axillary route. The incidence of fever (defined as rectal temperature ≥ 38.0°C, temperature by other routes ≥ 37.5°C) is documented in all study reports. In all studies except 711202/008 and 404286/006 a rectal temperature > 39.5°C or temperature > 39.0°C by other routes was graded 3 (severe). In studies -008 and -006 this level of fever was graded 2 and fever > 40.0°C (rectal) or > 39.5°C (other routes) was graded 3. In study 217744/074 a primary endpoint was the incidence of fever ≥ 40.0°C (rectal route).

For the purposes of this summary, for all studies except 404286/006 the incidence of grade 3 fever was calculated using a rectal temperature > 39.5°C or temperature > 39.0°C by other routes as the cut-off. For study 404286/006 the incidence of grade 3 fever was calculated using a rectal temperature 40.0 °C as the cut-off (i.e. a rectal temperature > 40.0°C = grade 3).

Follow up of large or extensive swelling reactions: In all of the studies except 208355/118 and 208355/120 large or extensive swellings were actively solicited. In the studies in which the event was solicited the characteristics of what were to be considered to be extensive swellings were defined in the protocol. With the exception of 455697/001 they were swelling with longest diameter > 50 mm, noticeable diffuse swelling, noticeable increase in limb circumference). For 455697/001 they were swelling with longest diameter > 50 mm or an increase of the limb circumference of > 50 mm as compared to a pre-vaccination measurement. Parents/guardians identifying such swellings were to contact the investigator and arrange for an examination.

Using a specific large/extensive swelling report form in the CRF, the diameter of any local swelling (if measurable, i.e. circumscribed) was to be noted, as was the diameter of any associated redness or induration. (It was anticipated that in some cases a discrete local swelling might be superimposed upon a diffuse swelling.) Also, the circumference of the vaccinated limb, and that of the opposite limb was to be measured. (In study 455687/001 comparison was made to limb circumference measured prior to vaccination).

The timing of onset, duration and outcome of the event were to be noted, and pain and functional impairment, if present, graded for severity. Temperature was to be recorded.

Pain was scored using the same criteria and the same four grades (from absent to severe, grades 0-3) as were routinely used when pain was solicited. Functional impairment was also scored on a four-grade scale. Impairment was to be scored as grade 3 (severe) when it prevented normal everyday activity.

Swellings were to be categorised by the investigator as:
i). local swelling around the injection site, not involving adjacent joints or
ii). diffuse swelling, not involving adjacent joints or
iii). swelling involving at least one adjacent joint. In some reports these categories have been respectively termed swelling "types" 1, 2 and 3. For reasons of brevity and clarity, the word "type" to identify swelling reactions has been adopted in this summary.

For studies 208355/118 and 208355/120 the protocol specified that parents/guardians were to contact the investigator immediately if the subjects manifested any signs or symptoms that raised their concern. Parents spontaneously contacting the investigator to report extensive local swelling were asked to present the child for an examination. The investigator was to document the characteristics of the swelling, and the temperature of the subject, on a specific form in the CRF. (The investigator was not asked to type or categorise the swellings in these two studies.) The date of onset and the date of resolution were to be recorded. The intensity (level of discomfort/interference with normal activities) was to be assessed. The circumferences of the injected and opposite limbs were to be recorded. The presence or absence of pain, redness and warmth were to be noted, and if any of these were present, a distinction made between localised and diffuse symptoms.

2.7.4.2.1.1 Common Adverse Events

Only those events that are pertinent to the variation application are summarised in this section. Although the variation relates specifically to the occurrence of large or extensive swelling reactions, a summary of data pertaining to all recorded swelling reactions (reported via the symptom sheets that were used by the parent or guardian to document solicited reactions) is also included, for comparative purposes.

The review of general solicited symptoms reported by parents or guardians using symptom sheets is limited to fever. Other general symptoms that were solicited are only addressed in this summary insofar as they are pertinent to this variation application.

Local and general solicited symptoms reported via symptom sheets after a booster dose of a Pa based combination vaccine

The frequency of reporting of swelling, pain and fever is presented, by study and for all studies combined, on the basis of prior vaccination history, in table 4.

Table 4 Reports of swelling, pain and fever in vaccinated subjects

Type of study	Study number	Local symptoms							General symptoms			
			Swelling		Pain		Grade 3 pain		Fever		Grade 3 fever	
		N	n	%	n	%	n	%	n	%	n	%
1st booster (3-dose primary course, Pa containing vaccine in 1st 6 months of life)*	208108/076	288	158	54.9	121	42.0	3	1.0	84	29.2	7	2.4
	213503/043	199	88	44.2	116	58.3	15	7.3	67	33.7	2	1.0
	213503/049	344	141	41.0	160	46.5	13	3.8	57	16.6	5	1.5
	217744/058	1138	317	27.9	354	31.1	60	5.3	458	40.2	35	3.1
	217744/059	440	158	35.9	171	38.9	28	6.4	207	47.0	20	4.5
	217744/061	193	54	28.0	72	37.8	1	0.5	62	32.1	3	1.6
	217744/062	228	89	39.0	109	47.8	12	5.2	102	44.7	9	3.9
	217744/065	173	59	34.1	67	38.7	7	4.0	83	48.0	10	5.8
	217744/066	82	32	39.0	35	42.7	4	4.9	34	41.5	6	7.3
	217744/095	329	114	34.7	109	33.1	7	2.1	109	33.1	9	2.7
	404286006	46	11	23.9	11	23.9	1	2.2	26	56.5	0*	0
	455697/001	161	72	44.7	94	58.4	12	7.5	63	39.1	5	3.1
	711202/008	459	113	24.6	97	21.1	3	0.7	103	22.4	3	0.7
	Overall (95%CI)	4080	1406	34.5 (33.0-35.9)	1516	37.2 (35.7-38.7)	166	4.1 (3.5-4.7)	1455	35.7 (34.2-37.2)	114	2.8 (2.3-3.3)
1st booster at 4-6 years of age following vaccination with Pa containing vaccine at 3, 5 and 11/12 months of age	213503/045	416	218	52.4	182	43.8	15	3.6	78	18.9	4	1.0
2nd booster at 4-6 years of age following primary and booster vaccination (4 doses) with Pa containing vaccine	208355/118	90	39	43.3	57	63.8	2	2.2	11	12.2	4	4.4
	208355/120	376	194	51.2	192	50.7	6	1.6	40	10.6	9	2.4
	213503/046	338	212	62.7	244	72.2	18	5.2	84	24.9	4	1.2
	Overall (95%CI)	804	445	55.3 (51.8-58.8)	493	61.3 (57.9-64.7)	26	3.2 (2.1-4.7)	135	16.8 (14.3-19.6)	17	2.1 (1.2-3.4)

N = Total vaccinated cohort for studies: 208108/076, , 213503/045, 213503/049, 217744/066, 217744/095, 404286/006 (group Z), 711202/008.
N = Subjects included in the ATP cohort for analysis of safety for studies: 208355/118, 208355/120, 213503/043, 213503/046, 217744/058, 217744/059, 217744/061, 217744/062, 217744/065, 455697/001.
This table does not include study 211774/074 as only fever and extensive swelling reactions were solicited.
*Grade 3 fever = > 40°C for this study.

The recorded incidence of solicited swelling (of any size) following a first booster dose in the 2nd year of life ranged (for the 13 studies) from 23.9% to 54.9%. The incidence of pain ranged from 21.1% to 58.4%, and of grade 3 pain from 0.5% to 7.5%. The reported incidence of fever ranged from 16.6% to 56.5% and of grade 3 fever from 0% to 7.3%.

Overall, reports of swelling followed 34.5% of first booster doses administered in the second year of life. Pain was reported following 37.2% of doses (graded 3 after 4.1% of doses). Fever was reported with an incidence of 35.7% (2.7% for grade 3).

One study (213503/045) documented the incidence of swelling, pain and fever after vaccination at 4 to 6 years of children who had previously received 3 doses of vaccine at 3,5 and 11 or 12 months of age. The reported incidence of (any) swelling was 52.4%, of pain 43.8% (3.6% grade 3) and of fever 18.9% (1.0% grade 3).

Three studies involved a 2nd booster dose at 4 to 6 years of age in children who had previously received 3 doses of vaccine in the first six months of life and a first booster in the second year of life, all with a Pa containing vaccine. The reported incidence of swelling ranged from 43.3% to 62.7%, the incidence of pain from 50.7% to 72.2% and of grade 3 pain from 1.6% to 5.2%. Fever was reported for 10.6% to 24.9% of vaccinees and grade 3 fever for 1.2% to 4.4%. Overall, there were reports of swelling (of any size) for 55.3% of vaccinees and of pain for 61.3% (grade 3 pain 3.2%). Fever was reported for 16.8% (2.1% grade 3).

Incidence of actively solicited reports of large or extensive swelling reactions after a booster dose of Pa based combination vaccine

The frequency of reporting of large swelling reactions after a first booster dose in the second year of life, a fourth vaccine dose between 4 and 6 years of age and a second booster dose at the same age is given in table 5.

Table 5 Incidence of extensive/large swelling reactions, by dose: all types combined

	N	n	%
1st booster dose after Pa priming in 1st 6 months of life	12306	326	2.6
1st booster dose after Pa administered at 3, 5, 11/12 months of age	416	63	15.1
2nd booster dose after Pa priming and 1st booster with Pa	362	92	25.4

Table includes "untyped" reactions and excludes studies-118 & -120

First booster in the second year of life.

Reports of large or extensive swelling reactions following a first booster dose in the 2nd year of life were solicited in all of the 13 studies that actively solicited swelling reactions of any size. In addition they were solicited in study 217744/074 which did not solicit smaller swelling reactions. In the 14 studies, large swelling reactions were reported for 326/12306 subjects in the total vaccinated cohort (2.6%).

The reported incidence, by study, of reactions meeting the defined criteria for large swelling reactions (all types combined, including those that were not typed), after a first booster dose with a Pa containing combination vaccine in the second year of life, ranged from 1.2% to 10.4% (table 6).

Table 6 **1st booster dose – Incidence of actively solicited large swelling reaction reports (all types combined, including unspecified types) following vaccination with a Pa containing vaccine, by study**

Study	Vaccine	N	n	%
208108/076	DTPa	69	12	
	DTPa/Hib	219	18	
213503/043	DTPa-IPV/Hib	200	15	7.5
213503/049	DTPa-IPV/Hib	344	21	6.1
217744/058	DTPa-HBV-IPV/Hib	693	13	
	DTPa-IPV/Hib	456	16	
217744/059	DTPa-HBV-IPV/Hib	443	15	3.4
217744/061	DTPa	96	1	
	DTPa-HBV-IPV	99	1	
217744/062	DTPa-HBV-IPV/Hib	237	4	1.7
217744/065	DTPa-HBV-IPV/Hib	175	5	2.9
217744/066	DTPa-HBV-IPV/Hib	82	1	1.2
217744/095	DTPa-HBV-IPV/Hib	329	4	1.2
217744/074	DTPa-HBV-IPV/Hib	4032	103	
	DTPa-IPV/Hib	4018	72	
404286/006	DTPa-HBV-IPV/Hib	191	6	3.1
455697/001	DTPa-IPV/Hib	163	13	8.0
711202/008	DTPa-HBV-IPV/Hib	459	6	1.3

N = Total vaccinated cohort

The incidence of reports of large swelling reactions after a first booster dose in the second year of life by study, vaccine and type of reaction is given in table 7.

Table 7 **Reaction reports by study, vaccine and type: 1st booster dose in the second year of life after Pa priming**

Study	Vaccine	N	Type 1		Type 2		Type 3		Type Unspecified	
			n	%	n	%	n	%	n	%
208108/076	DTPa	69	12	17.4	0	0.0	0	0.0	0	0.0
	DTPa/Hib	219	15	6.8	1	0.5	2	0.9	0	0.0
213503/043	DTPa-IPV/Hib	200	11	5.5	0	0.0	0	0.0	4	2.0
213503/049	DTPa-IPV/Hib	344	19	5.5	2	0.6	0	0.0	0	0.0
217744/058	DTPa-HBV-IPV/Hib	693	8	1.2	5	0.7	0	0.0	0	0.0
	DTPa-IPV/Hib	456	7	1.5	7	1.5	2	0.4	0	0.0
217744/059	DTPa-HBV-IPV/Hib	443	13	2.9	2	0.5	0	0.0	0	0.0
217744/061	DTPa	96	1	1.0	0	0.0	0	0.0	0	0.0
	DTPa-HBV-IPV	99	0	0.0	1	1.0	0	0.0	0	0.0
217744/062	DTPa-HBV-IPV/Hib	237	4	1.7	0	0.0	0	0.0	0	0.0
217744/065	DTPa-HBV-IPV/Hib	175	2	1.1	2	1.1	0	0.0	1	0.6
217744/066	DTPa-HBV-IPV/Hib	82	0	0.0	1	1.2	0	0.0	0	0.0
217744/095	DTPa-HBV-IPV/Hib	329	4	1.2	0	0.0	0	0.0	0	0.0
217744/074	DTPa-HBV-IPV/Hib	4032	73	1.8	28	0.7	2	0.05	0	0.0
	DTPa-IPV/Hib	4018	50	1.2	19	0.5	3	0.1	0	0.0
404286/006	DTPa-HBV-IPV/Hib	191	5	2.6	1	0.5	0	0.0	0	0.0
455697/001	DTPa-IPV/Hib	163	6	3.7	1	0.6	0	0.0	6	3.7
711202/008	DTPa-HBV-IPV/Hib	459	6	1.3	0	0.0	0	0.0	0	0.0

N = Total vaccinated cohort.

Document 1

CONFIDENTIAL

The incidence, of reaction reports (all types combined) following a first booster dose in the second year of life, by vaccine administered, is given in table 8.

Table 8 Large swelling reaction reports of all types by vaccine after 1st booster dose in the 2nd year of life

Vaccine	N	All reaction types combined	
		n	%
DTPa-HBV-IPV/Hib	6641	156	2.3
DTPa-IPV Hib	5181	127	2.5
DTPa-HBV-IPV	99	1	1.0
DTPa/Hib	219	18	8.2
DTPa	165	13	7.9

N = Total vaccinated cohort.

Fourth dose at 4 to 6 years of age.

One study (213503/045) actively solicited large swelling reactions following vaccination at between 4 and 6 years of children who had previously been vaccinated at 3, 5 and 11-12 months of age. The vaccines administered in this study were DTPa or DTPa-IPV. Reaction reports (all reaction types combined and both vaccines combined) were submitted for 63/416 subjects (15.1%). Table 9 gives the incidence of reports of large swelling reactions by vaccine and type of reaction. The incidence of swelling reports, for all reaction types combined, was 17.1% after DTPa and 13.3% after DTPa-IPV.

Table 9 Reaction reports by vaccine and type – 1st booster dose at 4-6 years after Pa administered at 3, 5, 11/12 months – study 213503/045

Vaccine	N	Type 1		Type 2		Type 3		Type unspecified	
		n	%	n	%	n	%	n	%
DTPa	205	27	13.2	5	2.4	3	1.5	0	0.0
DTPa-IPV	211	21	9.9	7	3.3	0	0.0	0	0.0

N = Total vaccinated cohort

Second booster dose at 4 to 6 years of age.

Three studies were carried out in this cohort; however, large swelling reactions were not solicited or assigned to a pre-determined swelling type in two of these studies 208355/118 and 208355/120.

In study 213503/046 a 2nd booster dose was administered to 362 children aged between 4 and 6 years who had previously received four doses of Pa based vaccine in the first two years of life. The vaccines administered were DTPa or DTPa-IPV. There were 92 reports of large swelling reactions (25.4%). Table 10 provides the incidence of reports from this study by vaccine and type of reaction. The incidence of reports, for all reaction types combined, was 27.1% after DTPa and 23.8% after DTPa-IPV.

Document 1

CONFIDENTIAL

Table 10 Reaction reports by vaccine and type – 2nd booster dose at 4-6 years after Pa priming and boosting in the first two years of life – study 213503/046

Vaccine	N	Type 1		Type 2		Type 3		Type unspecified	
		n	%	n	%	n	%	n	%
DTPa	181	30	16.6	9	5.0	10	5.5	0	0.0
DTPa-IPV	181	32	17.7	1	0.6	10	5.5	0	0.0

N = Total vaccinated cohort

Studies 208355/118 and 308355/120

There were nine spontaneous reports of swellings from parents or guardians in study 208355/118 (that followed the administration of DTPa as a second booster dose to 107 children aged 4 to 6 years. Of these, three would have been typed - based upon the investigator description of individual notable swellings - as type 2 or type 3 swellings. In study 208355/120 in which there were 26 spontaneous reports of swelling from 413 vaccinees of the same age who also received DTPa as a second booster dose. On the same basis of investigator description of notable swellings, one would have been assigned to type 3 and one to type 2 or 3.

Proportions of discrete (large) local swellings (not involving an adjacent joint) versus diffuse swellings and swellings involving an adjacent joint.

Table 11 summarises the relative proportions of reported discrete local (type 1) swellings versus larger type 2 and type 3 swellings after a first booster dose in the second year of life, a fourth vaccine dose at 4 to 6 years of age and a second booster dose at the same age for all vaccines combined.

Table 11 Reaction reports by vaccine dose and schedule – 1st booster dose in the 2nd year of life, vaccination at 4-6 years after 3, 5, 11/12 months and 2nd booster dose at 4-6 years

Vaccines and dose	N	Type 1 reaction reports		Type 2/3 reaction reports	
		n	%	n	%
1st booster in the 2nd year of life: Following vaccines combined: Hexa, DTPa-IPV/Hib, DTPa/Hib, DTPa-HBV-IPV, DTPa	315	236	74.9	79	25.1
1st booster dose at 4-6 years after 3, 5, 11/12 Following vaccines combined: DTPa-IPV, DTPa	48	63	76.2	15	3.6
2nd booster dose at 4-6 years Following vaccines combined: DTPa-IPV, DTPa	92	62	67.4	30	32.6

(Excludes -118 and -120 and reaction reports for which reaction type was not specified)
N = No of reports
n = number of reports of stated type

Table 12 breaks down the large swelling reports into two categories, discrete local type 1 versus type 2 and 3 swellings, by vaccine after a first booster dose in the 2nd year of life, a fourth dose at between 4 and 6 years of age and a 2nd booster dose at the same age.

Document 1

CONFIDENTIAL

Table 12 Relative proportions of reported Type 1 versus Type 2 & 3 reactions – reaction reports by vaccine and swelling types

Vaccine	N	Type 1 reaction report		Type 2 & 3 reaction report	
		n	%	n	%
1st booster dose in the 2nd year of life:					
DTPa-HBV-IPV/Hib	156	115	73.7	41	26.3
DTPa-IPV/Hib	127	93	69.9	34	30.1
DTPa/Hib	18	15	83.3	3	16.7
DTPa	13	13	100.0	0	0.0
4th dose at 4-6 years of age:					
DTPa-IPV	28	21	75.0	7	25.0
DTPa	35	27	77.1	8	22.9
2nd booster dose at 4-6 years of age:					
DTPa-IPV	43	32	74.4	11	25.6
DTPa	49	30	61.2	19	38.8

(Excludes -118 and -120 and reaction reports for which reaction type was not specified)
(DTPa-HBV-IPV = 1 report only, which was Type 2)
N = Number of reports
n = number of reports of stated type

All of the reported large swelling reactions were documented as having resolved.

The incidence of reported redness associated to large swelling reactions after a booster dose in the 2nd year of life was 87.1% (range across studies 75.0% to 100%). Induration was noted in 66.3% of reports (range 0.0% to 100%).

In the study that solicited large swelling reactions following a 4th dose at 4 to 6 years of age, the recorded incidence of redness was 95.6% and of induration 41.3%.

After a second booster dose at between 4 to 6 years the recorded incidence of redness (associated to actively solicited large swellings) was 98.9% and of induration 50.7%.

In all of the studies (whatever the dose administered or age of the vaccinees) in the majority of instances the time of onset of the event was recorded as being on the day of injection or on one of the following two days. The average recorded duration of the large or extensive swellings was approximately 3.5 days. The type of swelling did not influence the duration of the event.

Table 13 provides an overview of the reported incidence of grade 3 pain, grade 3 functional impairment and any and grade 3 fever for each reaction type by booster dose.

Doc ID REGU_20050A_8311

Table 13 Incidence and characteristics of reported large or extensive swelling reactions, by vaccine dose and reaction type

	Total cohort		Swelling		Swelling diameter (mean)	Difference in limb circumference (mean)	Grade 3 pain		Grade 3 impairment		Fever		Grade 3 fever	
			n	%			n	%	n	%	n	%	n	%
1st booster dose after 3 dose priming course in 1st 6 months of life	12306	Type 1	236	1.9	74.4	16.3	10	4.2	4	1.7	57	24.3	10	4.2
		Type 2	70	0.6	92.5	29.0	4	5.7	4	5.7	22	31.4	4	5.7
		Type 3	9	0.07	71.7	20.8	2	22.2	0	0.0	1	11.1	0	0.0
		Unspecif Type	11	0.08	73.5	36.9	0	0.0	0	0.0	2	18.2	0	0.0
Vaccine dose after vaccination at 3, 5, 11 months of age (1 study: 045)	416	Type 1	48	11.5	92.7	18.7	0	0.0	1	2.1	4	8.3	0	0.0
		Type 2	12	2.9	150.6	26.3	1	8.3	0	0.0	2	16.6	0	0.0
		Type 3	3	0.7	110.0	25.0	0	0.0	0	0.0	1	33.3	0	0.0
2nd booster dose after prior priming and booster vaccination with Pa (1 study: -046) (Excludes -118 & -120)	362	Type 1	62	17.1	76.6	20.8	3	3.2	1	1.6	6	9.7	0	0.0
		Type 2	10	2.8	89.9	28.3	0	0.0	0	0.0	0	0.0	0	0.0
		Type 3	20	5.5	116.5	35.2	2	10.0	1	5.0	3	15.0	0	0.0

N = No of reactions of specified type

* difference in circumference between the vaccinated limb and contra-lateral limb

GlaxoSmithKline Biologicals

2-7-4_Summary of Clinical Safety - Page 47

DTPa CTD, Module 2, Volume 1

Symptoms observed for subjects with large swelling reactions versus the total cohort

Table 14 summarises (by dose) the incidence of solicited reports of large or extensive swelling reactions and the incidence of solicited reports of all swellings including those that did not meet the defined criteria for large swellings.

Table 14 Solicited reports of swelling reactions: all swellings and large or extensive swellings

Vaccine dose	Proportion of vaccinees for whom swelling of any size or nature was reported	Proportion of vaccinees for whom a large/extensive swelling report was completed
4th dose (2nd year of life)	34.5%	2.6%
4th dose (4-6 years)	52.4%	15.1%
5th dose (4-6 years) (excludes -118 and -120)	62.7%	25.4%

Table 15 indicates the reported incidence of grade 3 pain associated to large or extensive swellings and to the total cohort. It also documents the incidence of reports of grade 3 fever for the two cohorts. For the large swelling reactions it documents the incidence of associated grade 3 functional impairment. (Functional impairment was solicited only in association with large swellings).

Doc ID RECU_20050A_83 1.1

Table 15 Solicited reports of swelling reactions, all swellings and large/extensive swellings – grade 3 pain, fever and impairment, by dose

	Incidence of Grade 3 pain		Incidence of Grade 3 fever		Incidence of Grade 3 impairment
Vaccine dose	within the cohort for whom swelling of any size was reported	within the cohort for whom large swelling reaction reports were completed	within the total vaccinated cohort	within the cohort for whom large swelling reaction reports were completed	within the cohort for whom large swelling reaction reports were completed
4th dose (2nd year of life)	4.1%	5.2%	2.7%	4.3%	2.5%
4th dose (4-6 years)	3.6%	0.2%	1.0%	0.0%	0.2%
5th dose (4-6 years) (excludes -118 and -120)	3.2%	4.3%	2.1%	0.0%	2.2%

2.7.4.2.1.2 Deaths

There were no reports of deaths during the course of any of the studies.

2.7.4.2.1.3 Other Serious Adverse Events

One swelling reaction was reported as a serious adverse event. This was in study 213503/049, a phase IV booster study in which children aged 17 to 20 months received DTPa-IPV/Hib vaccine as a first booster. This followed a primary vaccination course in which DTPa-HBV-IPV/Hib vaccine had been given at 2, 4 and 6 months either with or without concomitant administration of meningococcus type C conjugate vaccine. Vaccine was administered by IM injection into the anterolateral thigh.

The subject demonstrated grade 3 pain and grade 3 functional impairment. Two days after vaccination the child was hospitalised and a diagnosis of cellulitis was made. The investigator considered that there was a reasonable possibility that the SAE was due to the vaccine. There was no fever. The reaction had resolved by the fourth day after vaccination and the subject was discharged from hospital.

2.7.4.2.1.4 Other Significant Adverse Events

Not applicable

2.7.4.2.1.5 Analysis of Adverse Events by Organ System or Syndrome

Not applicable

2.7.4.2.2 Narratives

Not applicable

2.7.4.3 Clinical Laboratory Evaluations

Not applicable

2.7.4.4 Vital Signs, Physical Findings, and Other Observations Related to Safety

Not applicable

2.7.4.5 Safety in Special Groups and Situations

2.7.4.5.1 Intrinsic Factors

Not applicable

2.7.4.5.2 Extrinsic Factors

The impact of prior vaccination history has been addressed in Section 2.7.4.2.1.1

2.7.4.5.3 Drug Interactions

Not applicable

2.7.4.5.4 Use in Pregnancy and Lactation

Not applicable

2.7.4.5.5 Overdose

Not applicable

2.7.4.5.6 Drug Abuse

Not applicable

2.7.4.5.7 Withdrawal and Rebound

Not applicable

2.7.4.5.8 Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

Not applicable

2.7.4.6 Postmarketing Data

The database was searched (data lock point October 30, 2004) for all spontaneous reports of injection/application site reaction, local/general swelling and peripheral swelling. Reactions were classified as:

- "benign reaction" = redness or localised swelling
- "borderline reaction" = swelling > 5 cm (children < 2yrs) or > 10 cm (children > 2 yrs)
- "extensive reaction" = involving adjacent joint, severe, massive or extensive swelling or swelling of the whole injected limb.

Using the methodology and classification summarised above, 472 cases of extensive swelling reactions were retrieved. Most of these cases described swelling of the thigh or upper arm. However, some cases of swelling involved the entire injected limb, extending from the shoulder to the wrist or from the thigh to the foot, were reported. These latter cases represented less than 5% of all reported "extensive reactions".

Document 1

CONFIDENTIAL

The reporting frequency of "extensive reactions", by vaccine, is summarised in table 16.

Table 16 Reported frequency per 100,000 doses of "extensive reactions" by vaccine

Vaccine	Doses distributed since launch	Extensive swelling reports	Reporting frequency per 100 000 doses
DTPa	78 894 698	187	0.24
DTPa+HIB	12 209 138	76	0.62
DTPa-IPV	3 759 695	9	0.24
DTPa-HBV	5 806 271	4	0.07
DTPa-IPV+HIB	19 308 559	112	0.58
DTPa-HBV-IPV	8 983 906	1	0.01
DTPa-HBV-IPV+HIB	7 958 783	83	1.04

2-7-4_Summary of Clinical Safety_Appendix

2.7.4.7 APPENDIX

EXTENSIVE/LARGE SWELLING REACTIONS AFTER DTPA COMBINATION VACCINES

INFORMATION RECORDED ON THE SPECIFIC CRF PAGES

SUMMARY, FOR EACH SUBJECT, BY STUDY

In this appendix:

- "sub no" = subject number
- the column "mm diameter" provides the measured diameter, in mm, of any discrete swelling, whether or not this was superimposed upon a diffuse swelling
- "mm redness" and "mm induration" provide the diameter of any associated redness or induration
- the column "mm diff circum" provides the measured difference in mm of the circumference of the vaccinated limb and that of the contra-lateral limb, except in the case of study 455697/001, in which it was assessed against a day 0 measurement
- "duration" is the duration of the large or estensive swelling
- pain was graded on a scale from 0 (absent) to 3 (cried when the limb was moved/spontaneously painful)
- functional impairment was graded on a scale from 0 (absent) to 3 (prevents normal everyday activities)

Studies evaluating a first booster dose at 12-24 months of age

208108/076 (Hib-076). 1st booster at 12-18 months. DTpa coadministered with PRP or mixed with Hiberix. Pa primary.
DTPa coadministered with unconjugated. PRP: N= 69. **DTPa/Hib**: N= 219.

Vaccine	Swelling type	Sub no	Day onset	mm size	mm circum	Days duration	Outcome	mm redness	mm induration	Pain	Impair-ment	Fever °C
DTPa + PRP	Type 1	44	0	70	25	4	R	105	70	1	no	no
"	"	76	1	60	40	2	R	20	40	no	no	no
"	"	80	1	90	X	3	R	60	10	no	no	no
"	"	128	1	70	10	3	R	50	50	no	no	no
"	"	136	3	45	5	1	R	no	45	1	no	no
"	"	172	1	60	10	2	R	30	30	no	no	no
"	"	232	1	50	18	2	R	45	55	no	no	no
"	"	236	1	80	50	3	R	30	50	no	no	no
"	"	244	1	80	15	4	R	160	60	no	no	no
"	"	260	1	45	15	2	R	no	no	no	no	no
"	"	292	1	50	35	3	R	30	50	1	no	no
"	"	312	1	45	20	2	R	60	30	1	no	no

Site: deltoid. "X"= unknown. "R"= recovered. Fever = rectal ≥ 38°C; other routes ≥ 37.5°C.
(*No "unvaccinated limb" for subjects receiving PRP).
Cohort for N = vaccinated cohort. Extensive swelling = solicited.

208108/076 (Hib-076) continued.

Vaccine	Swelling type	Sub no	Day onset	mm size	mm circum	Days duration	Outcome	mm redness	mm induration	Pain	Impair-ment	Fever °C
DTPa/Hib	Type 1	22	1	55	10	3	R	55	no	no	no	no
"	"	59	1	70	20	2	R	70	60	no	no	no
"	"	67	1	40	10	3	R	50	40	2	no	no
"	"	117	1	50	25	3	R	85	50	no	no	no
"	"	129	1	70	10	3	R	40	40	no	no	no
"	"	153	1	50	10	5	R	20	no	no	no	no
"	"	163	1	60	6	4	R	60	60	2	1	no
"	"	175	1	60	10	3	R	60	20	2	no	no
"	"	182	2	60	20	3	R	30	30	no	no	no
"	"	271	1	80	20	5	R	40	40	no	no	no
"	"	298	1	60	17	2	R	64	no	no	no	no
"	"	306	1	50	20	3	R	50	40	no	no	no
"	"	326	1	52	14	3	R	60	28	1	no	no
"	"	337	2	60	20	3	R	50	50	no	no	no
"	"	339	1	80	30	7	R	70	70	no	no	no
"	Type 2	47	1	60	20	2	R	50	50	no	no	no
"	Type 3	99	0	70	5	3	R	60	no	no	no	no
	"	102	1	60	25	3	R	90	60	no	no	no

Document 1

213503/043 (DTPa-IPV-043). 1st booster dose at 17-19 months after a 3 dose primary series. DTpa-IPV/Hib (Hib TT Human or Hib TT Behring.) **(1). DTPa-IPV/Hib(TTH)**: N = 102. **(2). DTPa-IPV/Hib(TTB)**: N = 98. Pa priming.

Vaccine	Swelling type	Sub no	Day onset	mm size	mm circum	Days duration	Outcome	mm redness	mm induration	Pain	Impair-ment	Fever °C (route)
(1)	Local	249	2	90	5	4	R	90	90	1	no	no
"	"	284	2	70	25	5	R	50	35	1	no	no
"	"	349	2	-	50	6	R	70	no	no	no	no
"	"	419	1	80	10	2	R	80	no	no	no	37.6 O
"	"	575	2	60	50	17	R	60	no	1	no	no
"	"	583	1	70	50	4	R	70	no	1	no	38.6 A
"	NS	474	1	80	MC	4	R	12	no	2	no	no
"	"	562	2	90	90	9	R	90	90	2	no	38.0 O
(2)	Local	129	1	60	MC	1	R	MC	MC	-	-	-
"	"	274	2	60	15	4	R	60	60	2	no	no
"	"	410	1	150	10	3	-	160	150	1	no	no
"	"	461	1	100	MC	4	R	70	100	1	no	no
"	"	509	1	170	40	6	R	118	no	2	no	38.0 A
"	NS	41	1	80	20	2	R	80	80	1	no	no
"	"	712	3	MC	MC	7	R	no	no	no	no	no

Site: thigh. "NS" = type not specified. "-" = not available or not recorded. "MC" = missing confirmed. "R" = recovered. "O" = oral. "A" = axillary. Fever = rectal ≥ 38°C, other ≥ 37.5°C. Cohort for N = vaccinated cohort. Extensive swelling = solicited.

213503/049 (DTPa-IPV-049). 1st booster dose of **DTPa-IPV/Hib** at 17-20 months in children previously primed with Infanrix hexa administered concomitantly **(1)** with Meningitec (N = 173) or Infanrix hexa and Meningitec given at separate visits **(2)** (N = 169).

Vaccine	Swelling type	Sub no	Day onset	mm size	mm circum	Days duration	Outcome	mm redness	mm induration	Pain	Impair-ment	Fever °C (route)
(1)	Type 1	116	2	200	MC	4	R	15	no	2	3	no
"	"	137	1	60	-	3	R	60	60	no	no	no
"	"	177	1	70	MC	15	R	70	70	2	1	no
"	"	185	0	60	MC	3	R	60	60	1	no	no
"	"	212	1	60	-	2	R	60	-	1	no	no
"	"	215	1	60	-	2	R	60	no	1	no	no
"	"	216	2	60	-	1	R	80	no	1	no	no
"	"	232	1	100	-	2	R	120	no	1	no	no
"	"	342	2	60	-	1	R	60	60	2	no	no
"	Type 2	359	1	50	MC	2	R	2	50	no	no	no
"	"	506*	1	60	20	4	R	no	60	3	3	no
(2)	Type 1	127	1	60	-	3	R	60	no	no	no	no
"	"	140	0	80	-	7	R	20	80	3	2	38.0 Re
"	"	226	1	100	-	2	R	100	15	1	no	no
"	"	319	1	60	-	1	R	60	no	no	no	no
"	"	328	1	100	-	7	R	100	no	no	no	no
"	"	337	0	60	-	6	R	60	20	1	no	no
"	"	383	2	100	5	2	R	100	100	2	no	no
"	"	402	0	70	-	15	R	70	60	2	no	38.1 Re
"	"	405	1	55	-	1	R	60	-	1	no	no
"	"	489	1	60	-	1	R	60	no	1	no	no

Site: thigh. "-" = not available or not recorded. "MC" = missing confirmed. "R" = recovered. "Re" = rectal. Fever = rectal ≥ 38°C, other ≥ 37.5°C.
Cohort for N = vaccinated cohort. Extensive swelling = solicited.
(*SAE.)

217744/058 (DTPa-HBV-IPV-058). 1st booster at 12-18 months. 3 groups: Infanrix hexa, DTPa-IPV/Hib and DTPa-IPV/Hib+HBV. Pa primary. **(1) Infanrix hexa**: N = 693. **(2) DTPa-IPV/Hib**: N= 226. **(3) DTPa-IPV/Hib+HBV**: N: = 230

Vaccine	Swelling type	Sub no	Day onset	mm size	mm circum	Days duration	Outcome	mm redness	mm induration	Pain	Impair-ment	Fever °C *
(1)	Type 1	116	1	60	X	1	R	20	2	1	1	39.1
"	"	205	1	85	X	2	R	60	5	3	3	38.1
"	"	434	1	100	X	3	R	100	100	-	-	-
"	"	503	1	100	X	2	R	100	100	-	-	-
"	"	602	0	80	X	3	R	-	-	3	1	-
"	"	792	2	50	X	9	R	-	60	3	3	-
"	"	1095	1	80	20	2	R	-	80	-	-	-
"	"	1097	2	100	10	1	R	90	100	-	-	-
"	Type 2	181	1	250	X	3	R	5	-	2	1	38.7
"	"	182	1	250	X	4	R	3	-	2	1	38.5
"	"	547	1	180	16	3	R	50	-	-	-	39.8
"	"	678	2	50	X	3	R	4	-	1	-	38.2
"	"	1183	2	70	20	4	R	50	-	1	1	-
(2)	Type 1	144	1	70	25	2	R	70	60	2	-	-
"	"	492	1	100	X	2	R	100	-	-	-	-
	"	1192	2	70	X	3	R	70	70	-	-	39.6
"	Type 2	277	1	100	40	3	R	100	100	-	-	-
"	"	336	0	35	14	3	R	-	-	2	-	38.7
"	"	897	1	X	X	2	R	1	-	-	-	-
"	"	920	0	50	40	5	R	50	4	-	-	38.5
"	"	1103	1	70	X	3	R	70	-	3	-	39.7
"	Type 3	193	1	70	X	2	R	2	-	3	1	38.0
"	"	1188	2	100	X	1	R	100	-	2	-	-

Site: thigh. "-" = not reported or not present. "X" = unknown. "R" = recovered. Fever = rectal ≥ 38°C, other routes ≥ 37.5°C. *route is not specified. N = vaccinated cohort. Extensive swellings = solicited.

217744/058 (DTPa-HBV-IPV-058)continued

Vaccine	Swelling type	Sub no	Day onset	mm size	mm circum	Days duration	Outcome	mm redness	mm induration	Pain	Impair-ment	Fever °C
(3)	Type 1	168	0	90	X	2	R	90	90	-	-	39.6
"	"	171	1	250	X	3	R	50	-	-	-	38.1
"	"	363	1	60	X	2	R	10	-	2	-	-
"	"	779	1	50	10	4	R	-	10	-	-	-
"	Type 2	1091	1	100	X	3	R	100	-	1	-	-
"	"	1108	0	100	X	3	R	100	-	2	-	-

217744/059 (DTPa-HBV-IPV-059). 1st booster at 12-18 months. All Infanrix hexa. Pa primary.
Infanrix hexa: N = 443

Vaccine	Swelling type	Sub no	Day onset	mm size	mm circum	Days duration	Outcome	mm redness	mm induration	Pain	Impair-ment	Fever °C
Hexa	Type 1	103	1	80	5	2	R	30	60	2	-	40.4
"	"	133	0	100	10	1	R	110	100	2	-	38.5
"	"	195	0	60	5	2	R	10	-	1	X	-
"	"	236	1	95	30	5	R	95	-	-	-	38.3
"	"	288	1	140	X	2	R	140	2	2	-	-
"	"	353	2	60	15	2	R	60	60	-	-	-
"	"	422	2	40	X	8	R	50	-	2	X	-
"	"	425	1	50	X	3	R	100	50	2	-	-
"	"	436	1	50	0	7	R	30	50	-	1	-
"	"	438	1	120	27	3	R	118	220	1	2	-
"	"	439	1	50	0	5	R	50	50	-	-	-
"	"	442	1	50	0	3	R	70	50	-	-	-
"	"	488	3	80	X	2	R	80	80	2	2	38.4
"	Type 2	14	1	60	30	3	R	60	50	1	-	38.6
"	"	495	2	55	27	X	R	55	55	-	-	-

Site: thigh. "-" = not reported or not present "X" = unknown. "R" = recovered. Fever = rectal ≥ 38°C, other routes ≥ 37.5°C. Grade 3 fever > 39.5°C / > 39.0°C.
Cohort for N = vaccinated cohort. Extensive swellings = solicited.

217744/061 (DTPa-HBV-IPV-061). 1st booster at 15-18 months. DTPa or Infanrix penta. Concomitant with OmniHib. Pa primary.
DTPa: N = 96. **Infanrix penta** N = 99

Vaccine	Swelling type	Sub no	Day onset	mm size	mm circum	Days duration	Outcome	mm redness	mm induration	Pain	Impair-ment	Fever
DTpa	Type 1	035*	0	90	X	5	R	90	X	no	no	no
Penta	Type 2	004	1	70	35	5	R	90	-	-	-	-

Site: thigh. "-" = not reported "X" = unknown. "R" = recovered. Fever = rectal ≥ 38°C. Cohort for N = vaccinated cohort.
Extensive swellings = solicited.
(*No extensive swelling report for this subject).

217744/062 (DTPa-HBV-IPV-062). 1st booster at 12-15 months. All Infanrix hexa. Pa primary.
Infanrix hexa.: N = 237.

Vaccine	Swelling type	Sub no	Day onset	mm size	mm circum	Days duration	Outcome	mm redness	mm induration	Pain	Impair-ment	Fever °C (route)
Hexa	Type 1	4	0	55	20	2	R	55	55	3	2	38.0A
"	"	47	X	55	X	X	R	55	55	1	NM	NM
"	"	67	4	60	X	1	R	60	60	1	NM	NM
"	"	68	2	90	X	3	R	50	90	NM	NM	37.5 A

Site: thigh. "NM"= not measured. "X"= unknown. "R"= recovered. "A" = axillary. Fever = rectal ≥ 38°C, other routes ≥ 37.5°C.
Cohort for N = vaccinated cohort. Extensive swellings = solicited.

217744/065 (DTPa-HBV-IPV-065). 1st booster in 2nd year of life. All Infanrix Hexa. Coadministered Priorix/Varilirix or given alone Pa primary. **Infanrix hexa:** N = 175.

Vaccine	Swelling type	Sub no	Day onset	mm size	mm circum	Days duration	Outcome	mm redness	mm induration	Pain	Impair-ment	Fever °C
Hexa	Type 1	37	1	140	20	3	R	140	30	no	no	40.3
"	"	73	1	80	0	3	R	80	20	no	no	no
"	Type 2	226	1	120	X	6	R	110	no	1	1	no
"	"	228	5	80	2	3	R	70	no	2	no	no
"	NS	14	2	50	X	X	R	20	20	1	no	no

Sites: Hexa- thigh, concomitant vaccines- deltoid. "NS" = type not specified. "X" = unknown. "R"= recovered. Fever = rectal ≥ 38.0°C. Grade 3 fever > 39.5°C. Cohort for N = vaccinated cohort. Extensive swellings = solicited.

217744/066 (DTPa-HBV-IPV-066). 1st booster in 2nd year of life. All Infanrix hexa. Coadministered with HAV or given alone. Pa primary.
Infanrix hexa: N = 82.

Vaccine	Swelling type	Sub no	Day onset	mm size	mm circum	Days duration	Outcome	mm redness	mm induration	Pain	Impair-ment	Fever °C
Hexa	Type 2	38	1	80	X	2	R	10	10	2	2	no

Site for both vaccines: thigh. "X"= unknown. "R"= recovered. Fever = rectal ≥ 38.0°C.
Cohort for N = vaccinated cohort. Extensive swelling = solicited.

217744/074 (DTPa-HBV-IPV-074). 1st booster in 2nd year of life (previously primed with licensed vaccines according to vaccination recommendations in Germany). 2 groups: Infanrix hexa, (DTPa-HBV-IPV/Hib) and DTPa-IPV/Hib +HBV
(1) Infanrix hexa.: N = a). 4032, b). 3964. **(2) DTPa-IPV/Hib+HBV**: N = a). 4018, b). 3944.

Vaccine	Swelling type	Sub no	Day onset	mm size	mm circum	Days duration	Outcome	mm redness	mm induration	Pain	Impair-ment	Fever °C (route)
(1)	Local	181	1	50	MC	2	R	50	50	no	no	no
"	"	184	1	70	MC	6	R	70	70	2	no	39.5 R
"	"	261	1	100	MC	2	R	100	20	3	no	no
"	"	356	1	60	MC	2	R	60	no	no	no	no
"	"	424	1	70	10	4	R	70	60	2	no	38.4 Re
"	"	663	1	50	MC	2	R	3	50	no	no	MC
"	"	711	1	50	MC	1	R	50	50	1	1	no
"	"	775	1	30	50	3	R	50	30	2	1	37.7 A
"	"	902	1	100	30	4	R	2	100	3	3	no
"	"	933	1	70	40	4	R	70	10	no	no	-
"	"	1052	0	70	MC	4	R	70	50	2	no	38 0 Re
"	"	1184	0	55	MC	-	R	55	55	no	no	38.1 Re
"	"	1185	1	60	20	3	R	60	60	no	no	38.5 Re
"	"	1219	2	70	MC	1	R	70	-	no	no	MC
"	"	1274	1	80	MC	2	R	80	40	2	no	38.1 Re
"	"	1296	2	70	0	2	R	70	70	1	no	no
"	"	1588	1	80	MC	3	R	80	MC	no	no	no
"	"	1681	1	70	MC	1	R	70	3	no	no	no
"	"	1799	1	80	MC	2	R	N	80	no	no	no
"	"	1937	1	70	MC	2	R	70	70	1	1	-
"	"	1960	2	50	MC	3	R	50	20	no	no	-
"	"	1964	2	70	MC	3	R	38	20	no	no	380 Re
"	"	2093	1	150	MC	7	R	no	no	1	1	38.4 Re

Site: thigh. "Iv joint" = swelling involving joint. "MC" = missing confirmed, "R"= recovered, "-" = not recorded or not documented, "Y" = reported but with no size "A" = axillary. "Re" = rectal. Fever = rectal ≥38°C; other ≥37.5°C. Cohort for N = a). total cohort receiving vaccine, b). ATP cohort for the analysis of safety. Extensive swellings = solicited.

Document 1

217744/074 (DTPa-HBV-IPV-074) continued

Vaccine	Swelling type	Sub no	Day onset	mm size	mm circum	Days duration	Outcome	mm redness	mm induration	Pain	Impair-ment	Fever °C (route)
(1)	Local	2112	1	110	20	3	R	110	no	no	no	38.1 Re
"	"	2190	1	60	0	3	R	60	60	1	no	no
"	"	2291	1	80	20	3	R	80	50	no	no	no
"	"	2416	0	55	15	3	R	55	no	no	no	38.2 Re
"	"	2432	1	110	11	2	R	MC	MC	1	1	no
"	"	2437	1	65	10	3	R	65	65	2	no	no
"	"	2464	1	85	15	9	R	85	80	no	no	no
"	"	2483	0	100	MC	4	R	-	-	-	-	37.6A
"	"	2491	2	100	20	5	R	80	80	2	no	38.3 Re
"	"	2676	1	50	MC	8	R	50	50	1	no	MC
"	"	2677	1	75	30	6	R	75	75	no	no	no
"	"	2701	3	60	3	2	R	60	20	no	no	no
"	"	2734	1	61	MC	2	R	no	MC	no	no	no
"	"	2808	2	120	5	2	R	120	120	2	1	no
"	"	2830	1	70	MC	1	R	70	70	no	no	38.3 Re
"	"	2987	0	60	MC	4	R	60	no	no	no	no
"	"	3115	2	70	MC	3	R	70	no	2	no	no
"	"	3298	0	>50	MC	3	R	>60	>50	3	2	39.6 Re
"	"	3382	1	100	MC	3	R	100	no	no	no	MC
"	"	3495	2	60	10	5	R	60	30	no	no	no
"	"	3535	1	85	25	8	R	85	85	2	1	39.9 Re
"	"	3646	0	52	MC	2	R	no	52	no	no	38.1 Re
"	"	3650	1	60	20	2	R	60	40	2	2	no

217744/074 (DTPa-HBV-IPV-074) continued

Vaccine	Swelling type	Sub no	Day onset	mm size	mm circum	Days duration	Outcome	mm redness	mm induration	Pain	Impair-ment	Fever °C (route)
(1)	Local	3660	1	60	25	2	R	60	50	2	1	38.8 Re
"	"	3661	1	50	30	2	R	30	50	1	no	38.1 Re
"	"	3668	0	80	10	4	R	40	80	no	no	38.4 Re
"	"	3754	0	90	17	6	R	90	90	no	1	no
"	"	3836	1	80	10	4	R	80	70	1	no	no
"	"	4273	1	60	MC	2	R	60	50	2	no	38.5 Re
"	"	4711	2	100	20	4	R	100	100	2	no	no
"	"	4758	1	60	30	3	R	100	60	2	2	no
"	"	4772	0	80	30	3	R	80	no	1	no	no
"	"	4871	1	35	2	4	R	35	35	no	no	no
"	"	4988	2	60	10	3	R	60	60	2	1	no
"	"	5077	1	80	0	1	R	80	80	1	no	no
"	"	5712	1	60	MC	2	R	30	no	1	no	38.6 Re
"	"	5715	1	80	MC	7	R	no	80	no	no	38.1 Re
"	"	6126	1	130	30	3	R	130	130	no	no	-
"	"	6402	1	80	MC	4	R	140	80	2	1	38.9 Re
"	"	6491	0	60	15	5	R	60	60	2	no	39.2 Re
"	"	6579	1	120	45	4	R	120	120	1	2	38.4 Re
"	"	6626	1	40	5	4	R	20	10	1	no	no
"	"	6731	2	50	MC	13	R	50	5	no	no	no
"	"	6745	1	50	MC	3	R	50	50	no	no	no
"	"	7207	1	70	18	4	R	70	70	no	no	no
"	"	7500	1	100	10	2	R	N	30	1	no	no

217744/074 (DTPa-HBV-IPV-074) continued

Vaccine	Swelling type	Sub no	Day onset	mm size	mm circum	Days duration	Outcome	mm redness	mm induration	Pain	Impair-ment	Fever °C (route)
(1)	Local	7706	1	80	MC	2	R	80	no	2	1	no
"	"	8070	1	80	20	3	R	100	80	2	no	no
"	"	8255	1	50	30	2	R	50	50	2	no	39.2 Re
"	"	8319	1	60	MC	2	R	60	60	1	no	no
(1)	Diffuse	130	1	60	50	2	R	50	40	1	no	38.5 Re
"	"	203	2	100	MC	3	R	MC	-	-	no	no
"	"	204	1	140	30	2	R	MC	-	no	no	no
"	"	850	0	70	MC	6	R	70	30	2	1	39.0 Re
"	"	1606	1	70	29	2	R	70	25	2	1	38.8 Re
"	"	1992	1	80	30	4	R	50	30	2	1	no
"	"	2216	1	120	20	6	R	no	120	1	no	no
"	"	2289	2	MC	MC	3	R	MC	no	no	no	38.0 Re
"	"	2487	2	100	MC	2	R	100	no	1	no	no
"	"	3002	1	55	MC	3	R	MC	MC	no	no	no
"	"	3109	1	MC	MC	4	R	MC	no	2	2	no
"	"	3253	1	140	MC	3	R	140	40	no	no	no
"	"	3597	1	60	MC	3	R	60	50	2	1	38.2 Re
"	"	3826	1	150	40	8	R	150	100	no	no	no
"	"	3839	0	150	45	2	R	no	150	2	3	38.4 Re
"	"	3842	1	110	MC	6	R	110	no	1	no	no
"	"	5330	1	98	34	5	R	98	30	3	2	39.0 Re
"	"	5417	1	100	60	4	R	120	no	1	no	no
"	"	5663	1	120	5	3	R	120	80	2	no	no
"	"	6160	2	55	MC	5	R	50	50	no	no	no
"	"	6329	1	55	MC	2	R	no	55	1	no	no
"	"	6502	1	60	10	2	R	60	60	no	no	no
"	"	6747	2	30	30	4	R	no	no	no	no	no

217744/074 (DTPa-HBV-IPV-074) continued

Vaccine	Swelling type	Sub no	Day onset	mm size	mm circum	Days duration	Outcome	mm redness	mm induration	Pain	Impair-ment	Fever °C (route)
(1)	Diffuse	6836	1	50	20	2	R	100	no	no	no	39.0 Re
"	"	6887	2	110	40	5	R	110	no	no	1	no
"	"	7349	1	40	20	2	R	25	no	no	no	no
"	"	8135	1	170	25	4	R	60	no	no	no	38.1 Re
"	"	8297	1	150	MC	4	R	150	no	1	no	38.1 Re
(1)	Iv joint	5459	1	MC	20	2	R	no	no	no	no	no
"	"	7215	1	70	MC	3	R	MC	70	no	no	no
(2) combo	Local	379	0	60	5	3	R	60	50	no	no	no
"	"	461	1	80	MC	3	R	115	80	2	no	38.0 Re
"	"	544	0	70	MC	2	R	70	70	1	no	38.4 Re
"	"	545	1	70	MC	7	R	70	70	no	no	no
"	"	625	2	20	0	1	R	20	20	no	no	no
"	"	629	1	10	0	2	R	10	10	no	no	38.7 Re
"	"	1293	1	50	10	2	R	50	50	no	no	no
"	"	1772	1	120	20	5	R	120	100	no	no	no
"	"	1927	2	80	MC	2	R	N	no	no	no	no
"	"	2019	1	90	0	2	R	90	no	2	no	no
"	"	2415	1	70	20	3	R	70	30	no	no	38.2 Re
"	"	2444	1	60	10	2	R	60	60	2	no	38.2 Re
"	"	2490	1	60	MC	2	R	50	no	no	no	no
"	"	2855	2	150	MC	2	R	150	150	no	no	no
"	"	3300	0	>50	MC	3	R	>50	MC	3	2	no
"	"	3314	1	52	MC	1	R	52	no	no	no	no
"	"	3391	2	80	2	2	R	no	no	no	no	no
"	"	3651	0	55	10	3	R	55	30	1	no	no
"	"	3730	2	60	MC	2	R	60	no	no	no	no

217744/074 (DTPa-HBV-IPV-074) continued

Vaccine	Swelling type	Sub no	Day onset	mm size	mm circum	Days duration	Outcome	mm redness	mm induration	Pain	Impair-ment	Fever °C (route)
(2) combo	Local	3848	1	130	15	2	R	130	130	no	no	no
"	"	3863	1	85	20	3	R	30	no	1	no	no
"	"	3926	2	50	0	1	R	50	20	2	no	no
"	"	4011	1	150	MC	2	R	150	100	no	no	no
"	"	4041	0	>50	MC	3	R	>50	>50	2	2	38.8 Re
"	"	4089	3	51	-10	2	R	50	30	1	no	no
"	"	4154	1	60	MC	12	R	60	30	no	no	no
"	"	4370	1	180	10	4	R	80	40	no	no	39.7 Re
"	"	4468	1	70	MC	2	R	70	70	2	no	no
"	"	4475	1	70	MC	2	R	no	70	no	no	no
"	"	4648	1	50	MC	1	R	no	N	no	no	no
"	"	4770	0	60	10	4	R	60	40	1	no	no
"	"	4870	1	15	5	6	R	15	15	2	1	no
"	"	5254	1	75	2	3	R	75	45	2	no	-
"	"	5284	2	90	20	1	R	90	no	no	no	no
"	"	5536	2	42	20	2	R	no	no	no	no	no
"	"	5704	1	70	11	3	R	105	70	no	no	no
"	"	6724	2	90	MC	2	R	90	no	no	no	no
"	"	6799	0	80	MC	3	R	90	50	1	no	no
"	"	6809	2	120	10	3	R	120	120	no	no	no
"	"	6968	2	52	15	3	R	94	94	2	1	no
"	"	6966	2	85	10	2	R	85	85	2	1	no
"	"	7024	2	30	20	2	R	30	30	no	no	no
"	"	7221	1	70	MC	4	R	85	70	no	no	MC
"	"	7272	1	150	MC	4	R	150	150	1	2	39.6 Re
"	"	7440	1	50	MC	3	R	50	50	no	no	no

217744/074 (DTPa-HBV-IPV-074) continued

Vaccine	Swelling type	Sub no	Day onset	mm size	mm circum	Days duration	Outcome	mm redness	mm induration	Pain	Impair-ment	Fever °C (route)
(2) combo	Local	7632	0	80	10	2	R	80	50	2	1	no
"	"	7806	2	70	0	1	R	70	20	1	no	no
"	"	7807	1	80	25	2	R	80	30	1	no	MC
"	"	7817	1	90	MC	3	R	90	90	2	no	no
"	"	8588	1	55	MC	4	R	55	no	no	no	no
(2) combo	Diffuse	113	2	MC	MC	2	R	10	no	no	no	no
"	"	579	1	MC	MC	11	R	60	60	1	no	no
"	"	585	2	MC	MC	7	R	no	no	2	no	no
"	"	1215	0	110	MC	3	R	110	60	1	no	no
"	"	1613*	1	80	MC	4	R	60	60	2	no	no
"	"	2915	1	150	MC	3	R	150	150	no	no	no
"	"	3734	1	50	MC	2	R	MC	MC	Y	no	38.9 Re
"	"	4413	1	MC	MC	3	R	100	100	no	no	no
"	"	5029	2	85	30	6	R	no	85	2	no	no
"	"	6217	1	10	30	2	R	10	10	3	3	39.8 Re
"	"	6218	1	60	60	1	R	80	no	2	3	no
"	"	6492	2	100	14	5	R	100	100	1	1	no
"	"	6507	2	MC	25	1	R	no	70	no	no	no
"	"	7025	0	100	20	3	R	120	40	2	2	38.2 Re
"	"	7181	0	100	15	7	R	100	100	2	2	no
"	"	7496	1	120	6	3	R	80	20	2	no	no
"	"	8502	1	110	20	4	R	20	110	2	1	no
"	"	8508	1	100	10	14	R	100	no	no	no	no
"	"	8551	1	60	20	2	R	80	60	2	no	no
(2) combo	Iv joint	1488	1	MC	40	2	R	90	no	no	no	no
"	"	1745	0	MC	25	2	R	100	no	3	2	no
"	"	5323	0	60	10	5	R	no	no	no	no	no

*received DTPa-HBV-IPV/Hib due to randomisation failure

Document 1

217744/095 (DTPa-HBV-IPV-095). First booster dose at 11-23 months. **Infanrix hexa** to infants primed either with **(1) Hexavac** or **(2) Infanrix hexa.** N: group 1 = 163. N: Group 2 = 166.

Vaccine	Swelling type	Sub no	Day onset	mm size	mm circum	Days duration	Outcome	mm redness	mm induration	Pain	Impair-ment	Fever °C (route)
(1)	None											
(2)	Type 1	69	0	70	-	8	R	70	70	2	no	no
"	"	100	1	100	-	3	R	100	no	no	no	38.1 Re
"	"	358	1	60	-	2	R	90	no	3	no	38.1 Re
"	"	471	1	50	-	3	R	no	50	3	no	no

Site: thigh. "-" = not available or not recorded. "R" = recovered. "Re" = rectal. Fever = rectal ≥38°C, other ≥37.5°C
Cohort for N = vaccinated cohort. Extensive swelling = solicited.

404286/006 (DTPa-HBV-IPV/Hib-MenC[Hepta]-006). 1st booster in 2nd year of life. Previously primed with experimental vaccine containing a Pa component. DTPa-HBV-IPV/Hib co-administered with 1/5th of a dose of Mencevax **(1)** (N = 145) or alone **(2)** (N = 46)

Vaccine	Swelling type	Sub no	Day onset	mm size	mm circum	Days duration	Out-come	mm Redness	mm induration	Pain	Impair-ment	Fever °C (route)
(1)	Local	325	1	90	40	3	R	120	no	mild	no	38.2 Re
"	"	401	5	82	MC	9	R	82	no	mild	mild	38.6 Re
"	"	346	2	50	MC	2	R	50	no	mod	no	no
"	"	379	2	190	MC	6	R	82	no	no	no	no
"	Diffuse	23	1	230	80	3	R	90	60	mod	mod	no
(2)	Local	155	1	50	MC	2	R	50	no	no	no	39.9 Re

Site: thigh. "MC" = Missing Confirmed. "R" = recovered. "Re" = rectal. Fever = rectal ≥38°C.
Cohort for N = vaccinated cohort. Extensive swelling = solicited.

455697/001 (DTPa-HAV-IPV-001). 1st booster at 17-20 months. Pa primary.
(1) DTPa-IPV/Hib (given concomitantly with (2) HAV): N = 163.

Vaccine	Swelling type	Sub no	Day onset	mm size	mm circum	Days duration	Outcome	mm redness	mm induration	Pain	Impair-ment	Fever °C (route)
(1)	Type 1	18	1	60	0	2	R	no	no	no	no	no
"	"	48	1	120	10	3	R	120	120	2	no	37.6A
"	"	127	1	65	20	3	R	65	30	1	no	no
"	"	192	2	70	40	5	R	80	15	1	no	no
"	"	314	2	60	25	4	R	60	no	2	no	no
"	Type 2	228	2	12	14	2	R	30	20	2	no	37.6A
"	NS	240	2	90	30	2	R	90	no	2	no	no
"	"	264	1	100	40	3	R	60	no	1	no	no
"	"	271	2	45	40	1	R	40	no	1	no	no
"	"	284	2	20	30	2	R	80	no	2	no	no
"	"	311	1	100	25	3	R	120	no	2	no	no
(2)	Type 2	500	1	16	100	3	R	32	no	1	no	38.9A
(1) or (2)*	Type 1	290	1	70	20	2	R	40	no	2	no	no
"	NS	326	2	80	20	1	R	80	no	1	no	no

Site: thigh. "NS" = type not specified. "R" = recovered.
"A" = axillary. Fever = rectal ≥ 38°C, other ≥ 37.5°C. Cohort for N = vaccinated cohort. Extensive swelling = solicited. (*Arbitrarily assigned as DTPa-IPV/Hib for summary tables).

711202/008 (MenC-TT-008). 1st booster to children aged 12-15 months, previously primed with Infanrix penta or Infanrix hexa. All subjects received **(1)** Infanrix hexa concomitantly with 1/5th of a dose of Mencevax ACWY N = 459)

Vaccine	Swelling type	Sub no	Day onset	mm size	mm circum	Days duration	Out-come	mm Redness	mm induration	Pain	Impair-ment	Fever °C (route)
(1)	Type 1	171	1	50	-	2	R	70	-	1	no	no
"	"	462	2	40	-	4	R	6.0	-	no	no	no
"	"	415	2	80	-	3	R	no	-	no	1	38.1 Re
"	"	479	2	110	-	5	R	110	-	no	no	no
"	"	174	2	50	-	3	R	50	-	no	no	no
"	"	196	0	50	-	1	R	50	-	2	no	no

Site: thigh "R" = recovered. "-" = not recorded. "Re" = rectal. Fever = rectal ≥38°C.
Cohort for N = vaccinated cohort. Extensive swelling = solicited.

Document 1

CONFIDENTIAL

Studies evaluating a first booster dose at 4 - 6 years of age

213503/045 (DTPa-IPV-045). 4th dose at 4-6 years after 3,5,11-12 months. Two groups: DTPa-IPV and DTPa+IPV (IPV: Imovax Polio). Pa primary. **DTPa-IPV**: N = 211. **DTPa+IPV**: N = 205.

Vaccine	Swelling type	Sub no	Day onset	mm size	mm circum	Days duration	Outcome	mm redness	mm induration	Pain	Impair-ment	Fever °C (route)
DTPa-IPV	Local	42	0	MC	MC	3	R	MC	MC	-	no	MC
"	"	47	0	MC	MC	1	R	MC	MC	-	mild	MC
"	"	82	1	100	MC	4	R	100	MC	mod	no	no
"	"	87	0	130	MC	7	R	150	MC	mod	no	no
"	"	99	3	90	MC	7	R	100	MC	mod	no	no
"	"	113	1	65	MC	6	R	200	MC	mild	mild	no
"	"	117	1	100	MC	14	R	100	MC	mild	no	38.5 A
"	"	123	1	80	MC	5	R	100	MC	mod	no	37.9 Oth
"	"	134	1	60	MC	5	R	60	MC	mild	no	no
"	"	135	1	70	MC	1	R	30	MC	mod	mild	38.0 Oth
"	"	545	1	60	MC	3	R	70	MC	no	no	No
"	"	550	1	80	MC	5	R	120	MC	mild	no	No
"	"	139	1	MC	MC	5	R	MC	MC	-	no	MC
"	"	150	1	MC	MC	4	R	MC	MC	-	no	MC
"	"	170	2	MC	MC	5	R	MC	MC	-	no	MC
"	"	100	0	MC	MC	13	R	MC	MC	-	no	MC
"	"	590	1	MC	MC	3	R	MC	MC	-	no	MC
"	"	289	1	60	-	2	R	60	No	mild	no	no
"	"	335	1	100	MC	2	R	100	50	no	no	no
"	"	362	0	100	40	3	R	110	No	mod	no	no
"	"	426	2	90	0	2	R	100	No	mild	no	MC

Site: deltoid. (DTPa-IPV and DTPa left deltoid, Imovax right deltoid. "iv joint" = swelling involving joint. "-"=not reported or not present. "MC" = missing, confirmed. "R" = recovered. "A" = axillary, Re = rectal, "Or" = oral, "Oth"=other. Fever = rectal ≥38° C, other routes ≥ 37.5°C.
Cohort for N = Vaccinated cohort. Extensive swelling = solicited.

213503/045 (DTPa-IPV-045) continued

Vaccine	Swelling type	Sub no	Day onset	mm size	mm circum	Days duration	Outcome	mm redness	mm induration	Pain	Impair-ment	Fever °C (route)
DTPa-IPV	Diffuse	6	1	MC	MC	2	R	MC	MC	-	mild	MC
"	"	7	1	MC	MC	2	R	MC	MC	-	mod	MC
"	"	35	2	192	17	4	R	125	70	-	no	-
"	"	60	1	MC	MC	3	R	MC	MC	-	mod	MC
"	"	61	0	MC	MC	4	R	MC	MC	-	mild	MC
"	"	499	1	80	MC	2	R	80	40	mild	mild	MC
"	"	506	0	MC	32	2	R	70	no	mild	no	no
DTPa+IPV	Local	8	0	MC	MC	6	R	MC	MC	-	mild	MC
"	"	9	1	MC	MC	-	R	MC	MC	-	mild	MC
"	"	59	1	80	12	2	R	140	80	no	severe	no
"	"	95	1	80	MC	3	R	80	MC	mild	-	no
"	"	102	7	60	MC	57	R	80	MC	mild	no	no
"	"	114	1	150	MC	3	R	140	150	no	no	no
"	"	118	1	150	MC	3	R	150	MC	no	no	no
"	"	130	4	80	MC	3	R	70	MC	mod	no	no
"	"	131	0	200	MC	8	R	200	MC	mild	no	no
"	"	136	1	60	MC	15	R	80	MC	mild	no	no
"	"	541	1	70	MC	2	R	70	MC	mod	no	38.0 Re
"	"	549	1	100	MC	8	R	100	MC	mod	mild	no
"	"	140	1	MC	MC	5	R	MC	MC	-	no	MC
"	"	154	1	MC	MC	10	R	MC	MC	-	no	MC
"	"	156	1	MC	MC	2	R	MC	MC	-	no	MC
"	"	169	1	MC	MC	2	R	MC	MC	-	no	MC
"	"	176	1	MC	MC	1	R	MC	MC	-	no	MC
"	"	189	1	MC	MC	12	R	MC	MC	-	no	MC
"	"	202	1	MC	MC	11	R	MC	MC	-	no	MC

217744/045 (DTPa-IPV-045) continued.

Vaccine	Swelling type	Sub no	Day onset	mm size	mm circum	Days duration	Outcome	mm redness	mm induration	Pain	Impair-ment	Fever °C (route)
DTPa+IPV	Local	570	1	MC	MC	15	R	MC	MC	-	no	MC
"	"	572	1	MC	MC	9	R	MC	MC	-	no	MC
"	"	262	1	90	-	3	R	90	no	no	-	no
"	"	292	1	120	-	2	R	120	no	mild	no	no
"	"	364	1	75	MC	2	R	90	no	mod	no	no
"	"	438	1	100	40	2	R	65	no	mild	no	no
"	"	439	1	100	20	3	R	60	no	mod	no	no
"	"	420	3	80	0	1	R	80	50	mild	no	MC
DTPa+IPV	Diffuse	24	2	180	30	2	R	180	100	no	no	no
"	"	44	0	MC	MC	3	R	MC	MC	-	mod	MC
"	"	65	1	MC	MC	3	R	MC	MC	-	mod	MC
"	"	386	2	MC	MC	4	R	80	30	severe	mild	37.5A
"	"	433	1	MC	MC	1	R	150	80	no	no	37.5 A
"	lv joint	25	1	MC	MC	1	R	MC	MC	-	mild	MC
"	"	32	1	110	25	2	R	110	80	mild	mild	38.4Or
"	"	73	1	MC	MC	5	R	MC	MC	-	mod	MC

Document 1

CONFIDENTIAL

Studies evaluating a second booster dose at 4 - 6 years of age

208355/118 (APV-118). 5th (2nd booster) dose at 4 to 8 years. (4 doses Pa in the first 2 years of life). 3 groups, dTpa, DTPa and Td
DTPa: N = 107.

Vaccine	Swelling type	Sub no	Day onset	mm size	mm circum	Days duration	Outcome	redness	Warmth	Pain	Intensity swelling	Fever °C (route)
DTPa	"	83	-	-	X	2	-	local	local	local	2	no
"	"	86*	-	-	70	4	-	diffuse	diffuse	local	1	X
"	"	278	-	-	70	2	-	local	local	local	2	no
"	"	292*	-	-	25	4	-	local	local	local	2	38.0 Re
"	"	299	-	-	20	3	-	local	local	local	1	no
"	"	318*	-	-	60	4	-	local	local	local	1	no
"	"	329	-	-	40	4	-	diffuse	diffuse	diffuse	3	no
"	"	350	-	-	20	5	-	diffuse	diffuse	diffuse	3	no
"	"	358	-	-	30	2	-	diffuse	diffuse	diffuse	2	no

Site: deltoid. "NS" = type not specified. "-" = not available or not recorded "X" = unknown. "A" = axillary.
"Re" = rectal. Fever = rectal ≥ 38°C, other ≥ 37.5°C. Intensity swelling: 1: easily tolerated, 2: interferes with daily activities, 3: prevents normal activity/needs medical advice. (*Based upon the description in the study report, these are type 2/3 swellings.). Onset group 1: 0-1 days, group 2: 0-2 days, group 3: 1-32 days.
Cohort for N = vaccinated cohort. Extensive swelling = spontaneous reporting.

208355/120 (APV-120) 2nd booster at 4-6 years of age to children previously vaccinated with 4 doses of Infanrix (DTPa) in the first two years of life. **DTPa**: N = 413.

Vaccine	Swelling type	Sub no	Day onset	mm size*	mm circum	Days duration	Out-come	Redness	Warmth	Pain	Intensity Swelling	Fever °C (route)
DTPa	*NA	48	-	-	90	4	-	local	local	local	1	no
"	"	71	-	-	NR	4	-	local	diffuse	diffuse	2	-
"	"	82	-	-	NR	3	-	diffuse	no	no	2	no
"	"	86	-	-	30	3	-	diffuse	diffuse	diffuse	2	no
"	"	90	-	-	35	5	-	diffuse	diffuse	diffuse	2	no
"	"	111	-	-	160	4	-	diffuse	diffuse	diffuse	3	no
"	"	118	-	-	50	4	-	diffuse	diffuse	local	2	no
"	"	131	-	-	30	1	-	local	local	local	1	no
"	"	138	-	-	40	10	-	local	local	local	2	no
"	"	141	-	-	30	10	-	local	no	local	1	no
"	"	244	-	-	25	2	-	diffuse	local	local	1	no
"	"	245	-	-	20	2	-	local	local	local	1	no
"	"	250	-	-	15	3	-	diffuse	local	local	1	no
"	"	257	-	-	15	2	-	local	no	no	1	no
"	"	260	-	-	12	4	-	diffuse	no	no	1	38.7 Re
"	"	261	-	-	35	4	-	diffuse	diffuse	local	1	no
"	"	266	-	-	40	5	-	local	no	local	1	no
"	"	272	-	-	65	3	-	diffuse	diffuse	local	1	no
"	"	317	-	-	40	4	-	diffuse	diffuse	local	2	no
"	"	327	-	-	20	7	-	local	local	local	1	no
"	"	328	-	-	25	8	-	diffuse	local	local	1	no
"	"	402	-	-	37	4	-	diffuse	diffuse	diffuse	2	no
"	"	418	-	-	43	3	-	diffuse	diffuse	diffuse	2	37.6 O

*NA: not applicable. *Iv joint* = involving joint. *-* = not available or not recorded. *O* = oral. *Re* = rectal. Fever = rectal ≥38°C; other ≥37.5°C. Intensity of swelling: 1 = easily tolerated, 2 = interferes with daily activities, 3 = prevents normal activity/requires medical advice. Cohort for N = vaccinated cohort. Extensive swelling = spontaneous reporting.

208355/120 (APV-120) continued

Vaccine	Swelling type	Sub no	Day onset	mm size***	mm circum	Days duration	Out-come	Redness	Warmth	Pain	Intensity Swelling	Fever °C (route)
DTPa	°NA	437	-		20	4	-	diffuse	diffuse	local	1	37.5 O
"	Diffuse°	414	-		-	4	-	diffuse	diffuse	local	2	no
"	Iv joint°	419	-		20	4	-	diffuse	diffuse	local	2	no

° From clinical description in report text

213503/046 (DTPa-IPV-046). Single dose of DTPa-IPV and MMR vaccines to children 4-6 years of age who had previously received 4 doses of DTPa. 2 groups: **(1) DTPa-IPV + MMR**: N = 181. **(2): DTPa + IPV + MMR**: N = 181

Vaccine	Swelling type	Sub no	Day onset	mm size	mm circumf	Days duration	Outcome	mm redness	mm induration	Pain	Impair-ment	Fever °C (route)
(1)	Local	24**	1	70	MC	1	R	80	-	1	1	no
"	"	32	1	100	MC	5	R	100	-	2	no	no
"	"	55	2	60	MC	-	R	60	no	1	no	no
"	"	179	1	70	MC	4	R	70	no	1	no	MC
"	"	182	1	60	MC	2	R	60	no	1	no	MC
"	"	207	2	135	20	4	R	135	no	no	no	no
"	"	217	1	160	25	5	R	160	90	no	no	no
"	"	218	1	105	20	3	R	105	no	no	no	no
"	"	234	1	80	MC	1	R	1.0	no	no	no	no
"	"	239	2	80	10	2	R	40	10	no	no	37.5 A
"	"	242	1	55	MC	2	R	55	no	2	no	no
"	"	267	1	145	25	3	R	145	no	no	no	no
"	"	286	1	100	10	2	R	100	no	no	no	37.5 A
"	"	295	1	55	30	2	R	55	no	3	3	no
"	"	298	2	85	10	-	R	85	no	no	no	no
"	"	302	2	70	MC	1	R	70	-	1	no	38.0 A
"	"	328	3	55	10	2	R	-	55	no	no	37.6 A
"	"	331	2	60	0	2	R	60	no	2	1	no
"	"	334	1	55	10	2	R	50	35	1	1	no
"	"	383	0	90	15	3	R	100	no	1	1	no
"	"	384	1	70	35	2	R	80	no	no	no	no
"	"	403	2	60	MC	1	R	no	-	no	no	no
"	"	405	2	60	10	3	R	60	60	1	no	no

Site: deltoid. "Local" = local swelling > 50 mm diameter. "Iv joint" = swelling involving joint. "MC" = missing confirmed; "R"= recovered; "-" = not determined or not recorded, "Y" = reported but with no size, "A" = Axillary. Fever = axillary temperature ≥ 37.5°C. Cohort for N = vaccinated cohort. Extensive swelling = solicited. (** Prior vaccination history unknown).

213503/046 (DTPa-IPV-046) continued

Vaccine	Swelling type	Sub no	Day onset	mm size	mm circum	Days duration	Outcome	mm redness	mm induration	Pain	Impair-ment	Fever °C (route)
(1)	Local	412	1	100	MC	1	R	100	-	1	no	no
"	"	425	1	80	MC	1	R	80	-	3	2	MC
"	"	429	0	80	MC	3	R	80	-	2	1	MC
"	"	434	1	80	MC	2	R	80	-	1	1	MC
"	"	453	1	100	10	2	R	100	65	1	1	no
"	"	461	1	65	7.0	3	R	45	no	1	no	38.6 A
"	"	468	1	90	20	3	R	120	80	1	no	no
"	"	478	1	70	20	2	R	100	no	no	no	no
"	"	489	0	80	25	4	R	90	no	1	no	no
(1)	Diffuse	415	1	100	40	4	R	100	100	no	no	no
(1)	Iv joint	34	1	170	62	4	R	170	145	1	1	37.6 A
"	"	61	1	180	40	4	R	300	Y	1	no	MC
"	"	176	1	40	25	3	R	5.0	20	2	no	no
"	"	193	1	80	35	3	R	80	60	no	no	no
"	"	195	1	90	30	4	R	80	60	1	1	no
"	"	326	1	140	35	4	R	140	80	2	1	no
"	"	340	2	90	30	1	R	80	50	3	2	no
"	"	389	0	80	40	3	R	110	no	3	3	no
"	"	439	1	95	50	2	R	160	50	1	no	no
"	"	485	1	115	50	2	R	128	80	no	no	37.9 A

213503/046 (DTPa-IPV-046) continued

Vaccine	Swelling type	Sub no	Day onset	mm size	mm circum	Days duration	Outcome	mm redness	mm induration	Pain	Impair-ment	Fever °C (route)
(2)	Local	3	2	90	MC	1	R	90	80	no	1	no
"	"	17	0	60	-	3	R	140	no	1	no	38.1 A
"	"	18	1	100	-	3	R	100	-	2	2	no
"	"	23	1	70	MC	15	R	100	-	no	no	no
"	"	37	0	60	MC	3	R	60	-	no	no	no
"	"	53	1	145	35	4	R	100	145	1	no	MC
"	"	155	1	60	MC	2	R	90	no	no	no	no
"	"	163	1	100	25	-	R	100	-	no	no	no
"	"	165	1	80	MC	2	R	80	80	2	no	MC
"	"	205	1	60	5.0	7	R	60	no	1	no	no
"	"	214	2	80	10	5	R	80	no	no	no	no
"	"	220	2	100	10	2	R	100	no	no	no	no
"	"	240	1	75	30	2	R	75	no	no	no	no
"	"	241	1	70	-	2	R	70	-	2	no	no
"	"	282	1	130	30	7	R	130	70	1	no	no
"	"	318	1	50	20	2	R	40	no	no	no	no
"	"	321	1	50	20	3	R	60	no	1	no	no
"	"	333	1	65	10	3	R	65	no	no	no	no
"	"	341	2	60	MC	2	R	60	60	no	no	MC
"	"	404	1	60	15	3	R	90	40	2	2	no
"	"	407	1	90	70	6	R	90	60	1	1	no
"	"	422	1	40	14	3	R	70	20	1	1	no
"	"	431	1	50	15	2	R	60	no	no	no	no

213503/046 (DTPa-IPV-046) continued

Vaccine	Swelling type	Sub no	Day onset	mm size	mm circum	Days duration	Outcome	mm redness	mm induration	Pain	Impair-ment	Fever °C (route)
(2)	Local	441	1	80	26	2	R	100	20	1	1	no
"	"	452	1	70	MC	5	R	75	-	1	1	MC
"	"	456	1	65	10	3	R	90	50	no	1	no
"	"	457	1	80	MC	3	R	80	-	no	no	MC
"	"	464	1	85	85	2	R	95	85	1	1	no
"	"	475	2	70	20	6	R	105	70	no	no	no
"	"	481	1	-	30	3	R	70	-	1	no	MC
(2)	Diffuse	38	2	160	35	4	R	160	160	1	no	no
"	"	149	1	70	MC	5	R	70	-	2	no	no
"	"	172	1	130	20	3	R	130	130	1	no	no
"	"	290	1	55	10	3	R	65	no	no	no	no
"	"	296	1	65	20	18	R	50	no	no	no	no
"	"	335	1	70	50	1	R	-	no	2	1	no
"	"	382	1	75	24	1	R	90	no	no	no	no
"	"	438	1	90	45	2	R	120	no	no	no	no
"	"	440	2	75	11	2	R	105	60	1	no	no

213503/046 (DTPa-IPV-046) continued

Vaccine	Swelling type	Sub no	Day onset	mm size	mm circum	Days duration	Outcome	mm redness	mm induration	Pain	Impair-ment	Fever °C (route)
(2)	lv joint	62	1	210	35	7	R	150	no	2	2	no
"	"	167	1	90	10	3	R	90	30	1	no	37.8 A
"	"	216	1	90	20	2	R	100	no	1	no	MC
"	"	233	2	50	20	2	R	-	50	1	no	no
"	"	288	0	100	40	3	R	100	40	2	1	no
"	"	385	1	150	40	2	R	180	50	2	2	no
"	"	426	1	170	56	2	R	190	90	2	1	no
"	"	480	1	70	25	2	R	120	no	no	no	no
"	"	490	1	120	30	2	R	170	50	no	no	no
"	"	497	1	100	30	3	R	130	no	no	no	no

2-7-6_Synopses of individual studies

Document 1

CONFIDENTIAL

Module 2.7 : Clinical Summary

2.7.6 SYNOPSES OF INDIVIDUAL STUDIES

Doc ID REGU_200503_1172 1.1

CONFIDENTIAL

Tabular listing of all clinical studies

Study # (country)	Population / Age of subjects	Objectives	Type of study	DTPa combination vaccine evaluated*	N per group
208108/076 (Australia)	4th dose of a DTPa-combination – 12 – 18 months	Safety/Reactogenicity Persistence/Immunogenicity	Randomised Open	DTPa (+ PRP) DTPa/Hib	70 219
208355/118 (Germany)	5th dose of a DTPa-combination – 4-6 years	Safety/Reactogenicity Persistence/Immunogenicity	Randomised Single-blind	DTPa *dTpa* *Td (+ Pa/Ipa at month 1)*	107 *211* *103*
208355/120 (Germany)	5th dose of a DTPa-combination – 4-6 years	Safety/Reactogenicity Persistence/Immunogenicity	Open	DTPa	413
213503/043 (Lithuania)	4th dose of a DTPa-combination – 17-19 months	Safety/Reactogenicity Persistence/Immunogenicity	Randomised Double-blind (two Hib groups)	DTPa-IPV/Hib	200
213503/045 (Italy, Sweden)	4th dose of a DTPa-combination – 4-6 years of age	Safety/Reactogenicity Immunogenicity	Randomised Open	DTPa (+ IPV) DTPa-IPV	205 211
213503/046 (Australia)	5th dose of a DTPa-combination – 4-6 years of age	Safety/Reactogenicity Immunogenicity	Randomised Open	DTPa (+ IPV + MMR) DTPa-IPV (+ MMR)	181 181
213503/049 (Spain)	4th dose of a DTPa-combination – 17 – 20 months	Safety/Reactogenicity Persistence/Immunogenicity	Open	DTPa-IPV/Hib	344
217744/058 (Germany)	4th dose of a DTPa-combination – 12 – 18 months	Safety/Reactogenicity Persistence/Immunogenicity	Randomised Open	DTPa-IPV/Hib (+ HBV) DTPa-HBV-IPV/Hib	456 693
217744/059 (Switzerland)	4th dose of a DTPa-combination – 12 – 18 months	Safety/Reactogenicity Persistence/Immunogenicity	Open	DTPa-HBV-IPV/Hib	443
217744/061 (USA)	4th dose of a DTPa-combination – 15 – 18 months	Safety/Reactogenicity Persistence/Immunogenicity	Randomised Single-blind	DTPa (+ Hib) DTPa-HBV-IPV (+ Hib)	96 99
217744/062 (The Philippines)	4th dose of a DTPa-combination – 12 – 15 months	Safety/Reactogenicity Persistence/Immunogenicity	Open	DTPa-HBV-IPV/Hib	237
217744/065 (Germany)	4th dose of a DTPa-combination – 12 – 24 months	Safety/Reactogenicity Persistence/Immunogenicity	Randomised Open	DTPa-HBV-IPV/Hib (+ MMR or V)	175
217744/066 (Germany)	4th dose of a DTPa-combination – 12 – 24 months	Safety/Reactogenicity Persistence/Immunogenicity	Randomised Open	DTPa-HBV-IPV/Hib (+ HAV)	82
217744/074 (Germany)	4th dose of a DTPa-combination – 12 – 24 months	Safety	Randomised Open	DTPa-IPV/Hib (+ HBV) DTPa-HBV-IPV/Hib	4018 4032
217744/095 (Germany)	4th dose of a DTPa-combination – 11 – 23 months	Safety/Reactogenicity Persistence/Immunogenicity	Open	DTPa-HBV-IPV/Hib	329

GlaxoSmithKline Biologicals

Tabular listing of all clinical studies

Study # (country)	Population / Age of subjects	Objectives	Type of study	DTPa combination vaccine evaluated*	N per group
404286/006 (Germany)	4th dose of a DTPa-combination – 12 – 24 months	Safety/Reactogenicity Persistence/Immunogenicity	Randomised Open	DTPa-HBV-IPV/Hib (+ MenAC)	191
455697/001 (Lithuania)	4th dose of a DTPa-combination – 17 – 20 months	Safety/Reactogenicity Persistence/Immunogenicity	Randomised Open	DTPa-IPV/Hib (+ HAV) *experimental vaccine*	163 *331*
711202/008 (Germany)	4th dose of a DTPa-combination – 12 – 15 months	Safety/Reactogenicity Persistence/Immunogenicity	Open	DTPa-HBV-IPV/Hib (+ MenACWY)	459

*Vaccine abbreviations used:

DTPa	Diphtheria-tetanus-acellular pertussis	Infanrix
DTPa/Hib	Diphtheria-tetanus-acellular pertussis/*Haemophilus influenzae* type b	Infanrix+Hib
DTPa-HepB	Diphtheria-tetanus-acellular pertussis-hepatitis B	Infanrix-HepB
DTPa-IPV	Diphtheria-tetanus-acellular pertussis-inactivated polio	Infanrix-Polio or Infanrix-IPV
DTPa-IPV/Hib	Diphtheria-tetanus-acellular pertussis-inactivated polio/ *Haemophilus influenzae* type b	Infanrix-Polio/Hib or Infanrix-IPV+Hib
DTPa-HBV-IPV	Diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated polio	Infanrix penta
DTPa-HBV-IPV/Hib	Diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated polio/*Haemophilus influenzae* type b	Infanrix hexa
dTpa	low content diphtheria-tetanus-acelluar pertussis	
HAV	hepatitis A	
HBV	hepatitis B	
Hib	*Haemophilus influenzae* type b	
IPV	inactivated polio	
Men AC	unconjugated *N. meningitidis* polysachharide – serotypes A and C	
MenACWY	unconjugated *N. meningitidis* polysachharide – serotypes A, C, W and Y	
MMR	measles-mumps-rubella	
Pa/pa	tricomponent acellular pertussis (different formulations)	
PRP	unconjugated polyribosyl-ribitol-phosphate	
Td	adult formulation diphtheria-tetanus	
V	varicella	

Document 1

Name of Company: SmithKline Beecham Biologicals, Rixensart, Belgium Name of Finished Product: Name of active substance: DTPa, conjugated Hib, unconjugated PRP	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

Title of the study : 208108/076 (Hib-076)

Open, phase III clinical trial to assess the immunogenicity and reactogenicity of SB Biologicals' DTPa vaccine co-administered with one dose of unconjugated Hib vaccine in separate injections or mixed in the same syringe with SB Biologicals' Hib conjugate vaccine to healthy children, 12 to 18 months old, previously vaccinated at the age of 2, 4 and 6 months in study DTPa-HBV-IPV-036 (217744/036).

Principal Investigator:	s22 [redacted]
Study Center:	Clinical Epidemiology and Biostatistics Unit Royal Children's Hospital Research Institute Department of Paediatrics Parkville Victoria 3092, Melbourne, Australia

Publication (reference): Not published as of July 10, 2000

Study period: Date of first visit: September 4, 1999 Date of last visit: December 1, 1999	**Clinical phase:** III

Objectives:

Primary:

- To assess the immune memory to the Hib antigen induced by a three-dose primary vaccination course with SB Biologicals' DTPa-HBV-IPV/Hib vaccine through the immune response to the Hib antigen, 7 to 10 days after a booster dose of unconjugated Hib vaccine in Group 1.
- To assess the immune response to the Hib antigen 1 month after a booster dose of SB Biologicals' Hib conjugate vaccine, when administered with SB Biologicals' DTPa in one single injection in Group 2.

Secondary:

- To assess the immune response 1 month after a booster dose of SB Biologicals' DTPa vaccine when administered with SB Biologicals' Hib conjugate vaccine in one single injection in Group 2.
- To assess the reactogenicity of booster study vaccines.
- To assess the persistence of antibodies to all the antigens, 5 to 11 months after completion of the primary vaccination course with SB Biologicals' DTPa-HBV-IPV/Hib vaccine.

Methodology:

Study design: Open, randomised study, two parallel groups with unbalanced allocation (1:3) for booster groups.

Booster group 1 received DTPa + PRP and Booster group 2 received DTPa /Hib.

Subjects were primed at 2, 4, 6 months of age with either DTPa-HBV(cyst.)-IPV/Hib (Primary group 1) or DTPa-HBV(non cyst.)-IPV/Hib (Primary group 2) in study DTPa-HBV-IPV-036.

Number of subjects:

Planned:	368 (group 1 = 92, group 2 = 276)
Enrolled and completed:	289 (group 1 = 70, group 2 = 219)
Analysed for reactogenicity (ATP):	288 (group 1 = 69, group 2 = 219)
Analysed for immunogenicity (ATP):	278 (group 1 = 65, group 2 = 213)

Diagnosis and criteria for inclusion:

Healthy male or female children between the ages of 12 and 18 months at the time of booster vaccination, having received a complete primary vaccination course of DTPa-HBV-IPV vaccine co-administered with the Hib conjugate vaccine in study DTPa-HBV-IPV-036 and for whom prior written informed consent had been obtained.

Test product, dose, mode of administration, lot No.:

Vaccination schedule/site: Booster vaccination at 12 to 18 months of age.

Vaccines:

- SB Biologicals' combined diphtheria, tetanus, acellular pertussis (DTPa) vaccine containing per dose of 0.5 ml: ≥ 30 IU Diphtheria toxoid, ≥ 40 IU Tetanus toxoid, 25 mcg

Name of Company: SmithKline Beecham Biologicals, Rixensart, Belgium Name of Finished Product: Name of active substance: DTPa, conjugated Hib, unconjugated PRP	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

pertussis toxoid (PT), 25 mcg filamentous haemagglutinin (FHA), 8 mcg pertactin (PRN), ≤ 2.5 mg Phenoxyethanol and 150 mM Sodium Chloride. Lot 14866E9/M.

- SB Biologicals' *Haemophilus influenzae* type b lyophilised conjugate vaccine containing per dose of 0.5 ml (after reconstitution): 10 mcg Polyribosyl Ribitol Phosphate (PRP), 20-40 mcg Tetanus toxoid and 10 mg lactose. Lot Hib098A47/M.
- SB Biologicals' unconjugated PRP containing per dose of 0.5 ml (after reconstitution): 10 mcg PRP and 10 mg lactose. Lot DHib037A46.

Group	Visit	Vaccination	Route	Site	Side
1	1	DTPa unconjugated PRP	Intramuscular Intramuscular	Deltoid Deltoid	Left Right
2	1	DTPa *mixed with* Hib	Intramuscular	Deltoid	Left

Duration of treatment: Approximately one month per subject.

Reference therapy: Not applicable

Criteria for evaluation:

Immunogenicity: Measurement of antibody titres against each vaccine antigen prior to the booster dose and all except polio and HBs approximately one month after the booster dose. The primary endpoints were the percentage of subjects with anti-PRP ≥1.0 mcg/ml 7 to 10 days after vaccination with plain PRP (Group 1) and 30 to 48 days after vaccination with DTPa/Hib (Group 2). The secondary endpoints were seroprotection rates to D, T, HbsAg (pre-booster only), and poliovirus (Types 1, 2, 3)(pre-booster only), seropositivity and vaccine response rates for the pertussis components (PT, FHA, and PRN) and geometric mean titres (GMT) for antibodies against all vaccine antigens.

Safety: Recording of solicited local (redness, swelling and pain at each injection site) and general (diarrhoea, fever, irritability, loss of appetite, restlessness, sleeping more than usual and vomiting) symptoms by the parents/guardians during the 8 day follow-up period after vaccination. Recording of unsolicited adverse events, including serious adverse events (SAE) during the whole study period up to 30 days after the study vaccine administration.

Statistical methods:

The analysis was performed according to protocol.

Demographics: Demographics with respect to age, gender and race were tabulated.

Immunogenicity: Three analyses were done:

- Pre booster antibody persistence analysis for Post-primary and Pre-booster time-points for all antigens of the primary vaccine, according to the primary vaccination groups
- Post booster immunogenicity analysis for Post-primary, Pre- and Post-booster (day 7) time-points, for anti-PRP, for the subjects who received DTPa+PRP vaccine as booster

Immune response for Post-primary, Pre- and Post-booster (day 30) time-points for all antigens of the DTPa/Hib vaccine, for the subjects who received DTPa/Hib vaccine as booster

Immunogenicity was evaluated for each of the antigens in terms of GMTs and seropositivity/ seroprotection rates with their 95% confidence intervals (CIs). Vaccine response rates after vaccination were also calculated with their exact 95% CIs for the pertussis antigens.

Reactogenicity and safety: the percentage of subjects reporting any symptom within the 8 days following vaccination and their exact 95% CI were computed by booster group and overall according to the type of symptoms, their intensity and relationship to vaccination. The percentage of subjects reporting any unsolicited symptoms within 30 days following vaccination and their exact 95% CI were computed by booster group and overall after classification by WHO preferred term. SAEs were described.

SUMMARY-CONCLUSIONS:

Demography: The mean age of the subjects in the ATP immunogenicity cohort was 14.6 months. Majority (96%) of the subjects were white and male/female ratio was 134/144 overall.

Document 1

Name of Company: SmithKline Beecham Biologicals, Rixensart, Belgium Name of Finished Product: Name of active substance: DTPa, conjugated Hib, unconjugated PRP	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

Immunogenicity:

Table 1: Post-booster anti-PRP seroprotection rates and GMTs 7-10 days after the booster vaccination with unconjugated PRP, for the ATP immunogenicity cohort, were as follows:

Group Primary	Timing	N	≥ 0.15 mcg/ml				≥ 1 mcg/ml				GMT		
			n	%	95%CI		n	%	95%CI		mcg/ml	95%CI	
1	Pre Booster	38	29	76.3	59.8	88.6	10	26.3	13.4	43.1	0.457	0.298	0.701
	Post Booster (D7)	38	38	100	90.7	100	34	89.5	75.2	97.1	5.922	3.661	9.579
2	Pre Booster	26	21	80.8	60.6	93.4	6	23.1	9.0	43.6	0.437	0.257	0.742
	Post Booster (D7)	26	25	96.2	80.4	99.9	20	76.9	56.4	91.0	5.302	2.283	12.313
Either	Pre Booster	64	50	78.1	66.0	87.5	16	25.0	15.0	37.4	0.449	0.325	0.620
	Post Booster (D7)	64	63	98.4	91.6	100	54	84.4	73.1	92.2	5.662	3.677	8.719

Primary group 1: subjects primed with DTPa-HBV(cyst.)-IPV/Hib vaccine
Primary group 2: subjects primed with DTPa-HBV(non cyst.)-IPV/Hib vaccine
N = number of subjects with available results
n (%) = number (percentage) of subjects with titres within the specified range
Pre Booster = pre-booster blood sample
Post Booster (D7) = blood sample obtained 7-10 days after the booster vaccination.
95%CI = 95% confidence interval; GMT = Geometric mean titre

Overall, seven to ten days after a booster dose with unconjugated PRP vaccine, 98.4% of the subjects had antibody titres ≥ 0.15 mcg/ml. There was a 12-fold increase in anti-PRP GMTs from pre- to post-booster vaccination.

Table 2: Post-booster seroprotection rates and GMTs of anti-PRP antibodies one month after booster vaccination with conjugated Hib vaccine (administered with DTPa vaccine in a single injection); ATP immunogenicity cohort:

Group Primary	Timing	N	≥ 0.15 mcg/ml				≥ 1 mcg/ml				GMT		
			n	%	95%CI		n	%	95%CI			95%CI	
1	Pre Booster	98	79	80.6	71.4	87.9	33	33.7	24.4	43.9	0.494	0.380	0.642
	Post Booster (D30)	99	99	100	96.3	100	98	99.0	94.5	100	49.268	37.483	64.758
2	Pre Booster	113	98	86.7	79.1	92.4	31	27.4	19.5	36.6	0.550	0.440	0.686
	Post Booster (D30)	113	113	100	96.8	100	112	99.1	95.2	100	57.839	44.492	75.190
Either	Pre Booster	211	177	83.9	78.2	88.6	64	30.3	24.2	37.0	0.523	0.442	0.619
	Post Booster (D30)	212	212	100	98.3	100	210	99.1	96.6	99.9	53.665	44.462	64.773

Primary group 1: subjects primed with DTPa-HBV(cyst.)-IPV/Hib vaccine
Primary group 2: subjects primed with DTPa-HBV(non cyst.)-IPV/Hib vaccine
N = number of subjects with available results
n (%) = number (percentage) of subjects with titres within the specified range
Pre Booster = pre-booster blood sample
Post Booster (D30) = blood sample obtained 30 days after the booster vaccination.
95%CI = 95% confidence interval; GMT = geometric mean titre

Overall, one month after a booster dose with conjugated Hib vaccine (administered with DTPa vaccine in one single injection), all subjects had anti-PRP antibody titres ≥ 0.15 mcg/ml and 99% of the subjects had titres ≥ 1 mcg/ml. The GMTs increased 102-fold from the pre- to post-booster vaccination.

Table 3: Seroprotection rates and GMTs for anti-diphtheria and anti-tetanus antibodies and vaccine response rates and GMTs for anti-PT, anti-FHA and anti-PRN antibodies one month after booster vaccination with DTPa/Hib vaccine; ATP immunogenicity cohort:

Antigen	Unit	Timing	N	SPorVR				GMT		
				n	%	95%CI			95%CI	
Diphtheria	IU/ml	Pre Booster	210	122	58.1	51.1	64.8	0.130	0.114	0.147
		Post Booster (D30)	212	212	100	98.3	100	3.663	3.232	4.151
Tetanus	IU/ml	Pre Booster	209	181	86.6	81.2	90.9	0.224	0.200	0.252
		Post Booster (D30)	212	212	100	98.3	100	4.498	4.073	4.966
PT	ELU/ml	Pre Booster	208	-	-	-	-	7.6	6.8	8.5
		Post Booster (D30)	207	206	99.5	97.3	100	84.9	77.4	93.2
FHA	ELU/ml	Pre Booster	206	-	-	-	-	42.4	38.5	46.7
		Post Booster (D30)	203	202	99.5	97.3	100	604.2	542.2	673.4

Name of Company: SmithKline Beecham Biologicals, Rixensart, Belgium Name of Finished Product: Name of active substance: DTPa, conjugated Hib, unconjugated PRP	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

PRN	EIU/ml	Pre Booster	209	-	-	-	-	18.9	16.6	21.6
		Post Booster (D30)	208	208	100	98.2	100	551.7	482.4	631.1

SP = anti-diphtheria or anti-tetanus seroprotective titre (≥ 0.1 IU/ml)
VR = anti-PT, anti-FHA or anti-PRN vaccine response, defined as appearance of antibodies in prevaccination seronegative subjects and 2-fold increase in antibody titres in prevaccination seropositive subjects
N = number of subjects with available results; n (%) = number (percentage) of subjects with SP or VR
Pre Booster = pre-booster blood sample
Post Booster (D30) = blood sample obtained 30 days after the booster vaccination.
95%CI = 95% confidence interval; GMT = geometric mean titre

Table 4: Pre-booster antibody persistence (seroprotection/seropositivity rates):

				Primary group 1				Primary group 2			
Antigen	Cut-off	Unit	Timing	N	%	95%CI		N	%	95%CI	
Diphtheria	0.1	IU/ml	Post III	141	100	97.4	100	139	100	97.4	100
	0.016*	IU/ml	Pre Booster	144	98.6	95.1	99.8	140	99.2	96.1	100
Tetanus	0.1	IU/ml	Post III	141	100	97.4	100	139	100	97.4	100
			Pre Booster	143	84.6	77.6	90.1	139	87.7	81.1	92.7
PT	5	EIU/ml	Post III	141	100	97.4	100	139	100	97.4	100
			Pre Booster	143	79.0	71.4	85.4	138	73.2	65.0	80.4
FHA	5	EIU/ml	Post III	133	100	97.3	100	137	100	97.3	100
			Pre Booster	143	100	97.5	100	136	100	97.3	100
PRN	5	EIU/ml	Post III	141	100	97.4	100	139	100	97.4	100
			Pre Booster	143	90.9	85.0	95.1	139	94.2	89.0	97.5
HBs	10	mIU/ml	Post III	141	100	97.4	100	139	100	97.4	100
			Pre Booster	143	93.7	88.4	97.1	140	97.1	92.8	99.2
Polio 1	8		Post III	138	100	97.4	100	133	99.2	95.9	100
			Pre Booster	107	93.5	87.0	97.3	102	87.3	79.2	93.0
Polio2	8		Post III	135	97.0	92.6	99.2	132	99.2	95.9	100
			Pre Booster	110	92.7	86.2	96.8	103	88.3	80.5	93.8
Polio3	8		Post III	137	100	97.3	100	135	100	97.3	100
			Pre Booster	105	99.0	94.8	100	100	100	96.4	100
PRP	0.15	mcg/ml	Post III	140	97.9	93.9	99.6	139	97.1	92.8	99.2
			Pre Booster	144	80.6	73.1	86.7	140	85.7	78.8	91.1

N = number of subjects with available results
n (%) = number (percentage) of subjects with titres above or equal to the cut-off
Post III = blood sample obtained one month after the third dose of the primary vaccination
Pre Booster = pre-booster blood sample
95%CI = 95% confidence interval; GMT = geometric mean titre
*percentage of subjects with anti-diphtheria antibody titres ≥ 0.1 IU/ml by ELISA or ≥ 0.016 IU/ml on Vero-cell neutralization assay

Document 1

Name of Company: SmithKline Beecham Biologicals, Rixensart, Belgium Name of Finished Product: Name of active substance: DTPa, conjugated Hib, unconjugated PRP	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

Reactogenicity Results for the ATP reactogenicity cohort:

Table 5: Incidence of solicited local symptoms reported after the booster vaccination:

Solicited Local Symptoms		DTPa + PRP booster (N = 69)				DTPa/Hib booster (N = 218)			
		n	%	95%CI		n	%	95%CI	
Pain	Total	31	44.9	32.9	57.4	90	41.3	34.7	48.1
	Grade "3"	1	1.4	0.0	7.8	2	0.9	0.1	3.3
Redness	Total	48	69.6	57.3	80.1	143	65.6	58.9	71.9
	Grade "3"	27	39.1	27.6	51.6	79	36.2	29.9	43.0
Swelling	Total	40	58.0	45.5	69.8	118	54.1	47.3	60.9
	Grade "3"	20	29.0	18.7	41.2	58	26.6	20.9	33.0

N = Number of subjects with at least one local symptom sheet completed
n (%) = number (percentage) of subjects reporting a specific solicited local symptom (day 0-7)
95%CI = exact 95% confidence interval Total = Overall incidence of the specific symptom
Grade "3" pain = cries when the limb is moved/spontaneously painful
Grade "3" redness/swelling = greatest surface diameter > 20 mm

The most frequently reported solicited local symptom was redness at injection site. The percentage of subjects reporting grade "3" symptoms was similar between groups and the majority of the subjects reporting grade "3" solicited local symptoms recovered within the 8-day follow-up period after the booster vaccination.

Table 6: Incidence of solicited general symptoms reported after the booster vaccination:

Solicited General Symptoms		DTPa + PRP booster (N = 66)				DTPa/Hib booster (N = 208)			
		n	%	95%CI		n	%	95%CI	
Diarrhoea	Total	13	19.7	10.9	31.3	54	26.0	20.1	32.5
	Grade "3"	0	0.0	0.0	5.4	4	1.9	0.5	4.9
	PB/SU	12	18.2	9.8	29.6	30	14.4	9.9	19.9
Fever	Total	15	22.7	13.3	34.7	69	33.2	26.8	40.0
	Grade "3"	1	1.5	0.0	8.2	6	2.9	1.1	6.2
	PB/SU	5	7.6	2.5	16.8	37	17.8	12.8	23.7
Irritability	Total	32	48.5	36.0	61.1	113	54.3	47.3	61.2
	Grade"3"	0	0.0	0.0	5.4	6	2.9	1.1	6.2
	PB/SU	28	42.4	30.3	55.2	102	49.0	42.1	56.0
Loss of appetite	Total	22	33.3	22.2	46.0	61	29.3	23.2	36.0
	Grade"3"	1	1.5	0.0	8.2	6	2.9	1.1	6.2
	PB/SU	20	30.3	19.6	42.9	51	24.5	18.8	30.9
Restlessness	Total	24	36.4	24.9	49.1	79	38.0	31.4	45.0
	Grade"3"	2	3.0	0.4	10.5	3	1.4	0.3	4.2
	PB/SU	19	28.8	18.3	41.3	66	31.7	25.5	38.5
Sleeping more than usual	Total	12	18.2	9.8	29.6	47	22.6	17.1	28.9
	Grade"3"	0	0.0	0.0	5.4	5	2.4	0.8	5.5
	PB/SU	12	18.2	9.8	29.6	41	19.7	14.5	25.8
Vomiting	Total	4	6.1	1.7	14.8	20	9.6	6.0	14.5
	Grade"3"	0	0.0	0.0	5.4	3	1.4	0.3	4.2
	PB/SU	4	6.1	1.7	14.8	12	5.8	3.0	9.9

N = Number of subjects with at least one solicited general symptom sheet completed
n (%) = number (percentage) of subjects reporting a specific solicited general symptom (day 0-7)
95%CI = exact 95% confidence interval
Grade "3" irritability = crying/irritability that cannot be comforted Grade "3" fever = axillary temperature > 39°C
Other grade "3" adverse events = adverse events that prevented normal everyday activity
PB/SU= symptoms having a 'probable' or 'suspected' relationship to vaccination, as determined by investigator

Irritability was the most frequently reported solicited general symptom in both groups. The majority of the solicited general symptoms had a mild or moderate intensity. Most of the grade "3" symptoms were considered to have an 'unlikely' relationship to vaccination and the majority of the subjects reporting grade "3" symptoms recovered within the 8-day follow-up period.

Document 1

Name of Company: SmithKline Beecham Biologicals, Rixensart, Belgium Name of Finished Product: Name of active substance: DTPa, conjugated Hib, unconjugated PRP	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

Unsolicited symptoms: Out of 287 subjects with documented doses (ATP cohort), 128 subjects (39 in booster group 1, 89 in booster group 2) reported at least one unsolicited symptom (a total of 243 reports of adverse events classified by WHO Preferred Term: 71 in booster group 1 and 172 in booster group 2). Twenty-nine unsolicited symptoms were determined by the investigator to have PB/SU relationship to vaccination (13 in group 1 and 16 in group 2) and 40 were graded "3" in intensity. Majority of the symptoms resolved within the 30-day follow-up period.

Serious Adverse Events (SAEs): Three SAEs (subject n° 23, n° 67 and n° 99, all in booster group 2) were reported, all of which were determined by the investigator to be 'not related' or 'unlikely' to be related to vaccination. There were no withdrawals due to SAE.

Conclusions:

- The immune response 7 to 10 days after booster vaccination with unconjugated PRP vaccine indicated an anamnestic booster response and thus adequate priming with SB Biologicals' combined DTPa-HBV-IPV/Hib vaccine.
- Booster response one month after booster vaccination with DTPa/Hib, resulted in a 102-fold increase in anti-PRP GMTs and high seroprotection rates (100% ≥ 0.15 mcg/ml and 99 % ≥ 1.0 mcg/ml).
- One month after the booster dose, all subjects showed seroprotection for anti-diphtheria and anti-tetanus or were seropositive for anti-PT, anti-FHA and anti-PRN antibodies, with a vaccine response > 99% for anti-pertussis antibodies.
- Prior to booster vaccination, antibody GMTs and seroprotection/seropositivity rates to all antigens were similar for both primary vaccination groups.
- In both groups, the frequencies of any swelling, grade "3" swelling, and extensive swelling at the injection site were much higher than previously reported in the literature for either DT, DTPw or DTPa vaccines. This increase may be due to improved ascertainment using active surveillance methods. The frequency of swelling following DTPa vaccination should be assessed in future studies, using both the active surveillance methodology from this study and the standard passive surveillance mechanism used routinely.
- The DTPa/Hib vaccine showed an acceptable safety and reactogenicity profile when given as a booster dose in the second year of life.

Date of report: July 10, 2000
Date of corrigendum: September 14, 2000

Document 1

Name of Company: SmithKline Biologicals, Rixensart, Belgium Name of Finished Product: Name of active substance: 208355/DTPa vaccine	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

Title of the study : 208355/118 (APV-118)
Randomised, blinded clinical study to assess the immunogenicity and reactogenicity of SB Biologicals' dTpa and DTPa vaccines and a commercial Td vaccine administered as a booster dose to healthy children 4 to 6 years old, previously vaccinated with four doses of SB Biologicals' DTPa vaccine in the first two years of life.

Investigators : s22 [redacted]

Study centre(s): Kinderklinik, Johannes-Gutenberg-Universität
Langenbeckstraße 1
55101 Mainz, Germany

Publication (reference): Not Applicable

Studied period: Started: January 3, 1998
Ended: May 19, 1998

Clinical phase: IIa

Objectives:
The primary objective of the Study APV-118 was

- To assess and compare the immunogenicity of a booster dose of SmithKline Beecham (SB) Biologicals' dTpa and DTPa vaccines, in terms of the humoral immune response to the three pertussis antigens (pertussis toxin [PT], filamentous haemagglutinin [FHA] and pertactin [PRN]) one month after the booster vaccination.

The secondary objectives were

- To assess and compare the immunogenicity of SB Biologicals' dTpa and DTPa vaccines and the Td vaccine in terms of the humoral immune response to the diphtheria and tetanus toxoids, one month after the booster vaccination.
- To assess and compare the reactogenicity after administration of the study vaccines.
- To assess the persistence of antibodies to the three pertussis antigens, diphtheria and tetanus, immediately prior to the booster dose.
- To assess the immunogenicity of SB Biologicals' dTpa and DTPa vaccines, in terms of the cell-mediated immunity (CMI) to the three pertussis antigens before and one month after the booster dose. (The results of the CMI analysis will be presented in an annex report.)
- To asses the safety and reactogenicity of a single dose of SB Biologicals' pa vaccine as compared with the licensed Pasteur Mérieux acellular pertussis vaccine (Pa: Pac Mérieux®) in subjects previously administered Td vaccine. (The results of this analysis will be presented in an annex report.)

Methodology:
Design: Randomised, blinded comparative, monocentre booster study with three groups:

- One group received the dTpa vaccine.
- A second group received the DTPa vaccine.
- A third group received the Td vaccine and either candidate pa vaccine or commercial Pa vaccine at least one month later (administration of the pa/Pa vaccine was an annexe phase).

The study was single blind for all groups.

Name of Company: SmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** **Name of active substance:** 208355/DTPa vaccine	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Number of subjects (total and for each treatment):
Enrolled: 422 Completed: 418
ITT analysis for reactogenicity and immunogenicity: 421
(211 in dTpa group; 107 in DTPa group; 103 in Td group)
ATP analysis for reactogenicity: 357
(180 in dTpa group; 90 in DTPa group; 87 in Td group)
ATP analysis for immunogenicity: 336
(172 in dTpa group; 83 in DTPa group; 81 in Td group)

Diagnosis and criteria for inclusion:

- Subject must have been vaccinated with four doses of SB Biologicals' DTPa vaccine in their first two years of life in SB Biologicals' studies APV-039 and APV-039B.
- Subject must have been healthy and between 4 and 6 years of age at the time of vaccination.
- Written informed consent must have been obtained from the parents/guardian of the subject.

Test Vaccines, dose, mode of administration, batch No.:
Vaccination schedule: dTpa group: one dose at visit 1: DTPa group: one dose at visit 1; Td group: one dose of Td at visit 1 and one dose of either pa or Pa at least one month later
Route: Intramuscular injection in the deltoid region (left arm for dTpa, DTPa and Td; right arm for pa and Pa).
The following test products were used in this study: SB's combined diphtheria-tetanus-acellular pertussis (dTpa) vaccine: SB's acellular pertussis vaccine (pa).

Vaccine	Lot	PT antigen	FHA antigen	PRN antigen	Diphtheria toxoid	Tetanus toxoid
dTpa	37711A2	8 mcg	8 mcg	2.5 mcg	≥ 2 IU (2.5 Lf)	≥ 20 IU (5 Lf)
pa	DPSK321A2	8 mcg	8 mcg	2.5 mcg	-	-

PT = pertussis toxoid; FHA = filamentous haemagglutinin; PRN = pertactin

Reference vaccines, dose, mode of administration, batch No.:
Dose and route of administration: see above
The following commercial products were used in this study: SmithKline Beecham Biologicals' DTPa vaccine (Infanrix™); Chiron-Behring's combined diphtheria and tetanus vaccine (Td-pur®); Pasteur Mérieux MSD's licensed Pa vaccine (Pac Mérieux®)

Vaccine	Lot	PT antigen	FHA antigen	PRN antigen	Diphtheria toxoid	Tetanus toxoid
Infanrix™	820A2/M	25 mcg	25 mcg	8 mcg	≥ 30 I.U (25 Lf)	≥ 40 I.U (10 Lf)
Td-pur®	001141	-	-	-	≥ 2 I.U	≥ 20 I.U.
Pac Mérieux®	7B91495	23.4 mcg	23.4 mcg	-	-	-

Document 1

Name of Company: SmithKline Biologicals, Rixensart, Belgium Name of Finished Product: Name of active substance: 208355/DTPa vaccine	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

Criteria for evaluation:

Immunogenicity: Determination of the antibody titres against diphtheria and tetanus toxoids, as well as against PT, FHA and PRN, prior to and one month after vaccination.

Serum antibody titres against pertussis antigens were determined by ELISA with a cut-off of 5 EU/ml. Antibodies to diphtheria and tetanus toxoids were measured by ELISA with a cut-off of 0.1 IU/ml. Anti-diphtheria titres < cut-off of ELISA were re-tested by the more sensitive VERO test with a cut-off of 0.016 IU/ml. A vaccine response to the pertussis antigens was defined as the appearance of an antibody titre > cut-off in initially seronegative subjects, or as at least a two-fold increase of a positive pre-vaccination titre. For GMT (geometric mean of titres) calculations, antibody titres below the cut-off of the assay were given an arbitrary value of half the cut-off.

Determination of the cell-mediated immune response (CMI) to each of the pertussis antigens (specific lymphoproliferation, interferon gamma [IFN-γ] and interleukin 5 [IL-5] secretion).

Reactogenicity: Incidence by group of any symptoms, local and general symptoms, after vaccination, in addition to occurrence of each individual local solicited symptom by onset (with intensity), general solicited symptoms by onset (with intensity and relationship), and unsolicited symptoms (with intensity and relationship), and serious adverse events. Follow-up period for solicited symptoms was days 0-14, for unsolicited symptoms, days 0-30, and for serious adverse events during the clinical trial or within 30 days following administration of the study vaccine.

Statistical methods:

Immunogenicity: for each vaccine group, the seropositivity rates/vaccine response rates one month after vaccination and their 95% CIs were calculated; antibody titres were summarised by GMTs, their 95% CIs and reverse cumulative distribution curves.

As per protocol, the null hypothesis of no treatment difference between dTpa and the control vaccines (DTPa and Td) was evaluated using a two-sided test with 0.0167 alpha level:

- Fisher's exact test was used for comparing seropositivity rates/vaccine response rates
- t-te
- st on the log-transformed antibody titres, or Wilcoxon test in case normality assumptions were not fulfilled

However, since the objective of the study was to rule out a decrease in immunological response rather than to demonstrate a difference, focus was made on the upper limit of the 90% CI for vaccine difference in seropositivity rates/vaccine response rates and for the GMT's ratios. The 90% CI for the GMT ratios were primarily obtained from an ANOVA model on the logarithm of the titres and secondarily from a Cox regression on the titres.

The current sample size of 168 subjects in dTpa group and 79 subjects in DTPa group (number of subjects evaluable for pertussis vaccine response) had 90% power to reject the null hypothesis that, as compared to DTPa, dTpa decreases the proportion of subjects with a vaccine response to PT, FHA or PRN by at least 5.7%, 10.3% or 7.4%, respectively (one-sided test; alpha = 0.05; Bonferroni adjustment for three primary endpoints; power under the hypothesis that the response rates are 98.5% for PT, 95% for FHA, and 97.5% for PRN; Nquery equivalence of proportions).

Reactogenicity: the percentages of subjects reporting symptoms within the 15 days following vaccination and their 95% confidence intervals (CIs) were computed by vaccine group. The overall percentages of subjects with at least one symptom reported during the 15-day follow-up period whether solicited or not (any, local and general, respectively) were compared between dTpa and each control vaccine group using two-sided Fisher's exact tests with 0.0167 alpha level. The difference in incidence was also evaluated using exact 90% CI. Finally, the Spearman correlation coefficients between pre-vaccination anti-diphtheria, anti-tetanus, anti-PT, anti-FHA and anti-PRN antibody titres and the intensity of swelling reported during the 15-day follow-up was evaluated in each vaccine group.

Name of Company: SmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** **Name of active substance:** 208355/DTPa vaccine	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Summary:

(Note: CMI results and results concerning pa and Pa vaccines will be presented separately in an annex report.)

Immunogenicity (ATP cohort) (see Tables 1, 2. 3 and 4)

- Most subjects in each group showed a vaccine response to each of the pertussis antigens: however, the vaccine response to FHA tended to be higher in the DTPa group than in the dTpa group.
- All subjects in both groups had antibody titres ≥ 5 EU/ml for each of the pertussis antigens one month after vaccination.
- Post-vaccination, anti-pertussis (anti-PT, anti-FHA and anti-PRN) GMTs were similar, as were the distribution of titres, in the DTPa and dTpa groups.
- All subjects had post-vaccination anti-diphtheria and anti-tetanus titres ≥0.1 IU/ml. Most subjects had post-vaccination anti-diphtheria and anti-tetanus titres ≥1.0 IU/ml: 99.4%, 100% and 97.5% for anti-diphtheria titres in the dTpa. DTPa and Td groups, respectively; 98.3%, 100% and 100% for anti-tetanus titres in the dTpa, DTPa and Td groups, respectively.
- Anti-diphtheria GMTs tended to be similar following dTpa and Td vaccination and highest following DTPa vaccination. Anti-tetanus GMTs tended to be similar following dTpa and DTPa vaccination and highest following Td vaccination.
- Persistence of antibodies prior to the booster dose: approximately half of the subjects in the dTpa and DTPa groups were seropositive (titres ≥ 5 EU/ml) for anti-PT antibodies and most were seropositive for anti-FHA and anti-PRN antibodies before vaccination (no analysis was done for pertussis antigens in subjects receiving Td vaccine). More than 84% of subjects in each group had pre-vaccination anti-diphtheria antibody titres ≥0.1 IU/ml (ELISA) and more than 80% had pre-vaccination anti-tetanus antibody titres ≥0.1 IU/ml (ELISA).

Document 1

Name of Company: SmithKline Biologicals, Rixensart, Belgium Name of Finished Product: Name of active substance: 208355/DTPa vaccine	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

Table 1 Vaccine response rates, seropositivity rates and geometric mean titres (GMT) for anti-PT, anti-FHA and anti-PRN antibodies for the ATP Cohort for Immunogenicity Analysis

Group	Timing	N	VR			S+			GMT	(EU/ml)
			n	%	[95%CI]	n	%	[95% CI]	Value	[95%CI]
Anti-PT										
dTpa	Pre	172	-	-	-	83	48.3	[40.6, 56.0]	5	[4, 6]
	Post	172	169	98.3	[95.0, 99.6]	172	100.0	[97.9, 100.0]	64	[57, 72]
DTPa	Pre	83	-	-	-	42	50.6	[39.4, 61.8]	5	[4, 6]
	Post	83	82	98.8	[93.5, 100]	83	100.0	[95.7, 100.0]	79	[68, 92]
Anti-FHA										
dTpa	Pre	169	-	-	-	162	95.9	[91.7, 98.3]	70	[57, 86]
	Post	171	153	91.1	[85.7, 94.9]	171	100.0	[97.9, 100.0]	764	[690, 845]
DTPa	Pre	79	-	-	-	77	97.5	[91.2, 99.7]	60	[44, 80]
	Post	83	78	98.7	[93.1,100]	83	100.0	[95.7, 100.0]	862	[748, 995]
Anti-PRN										
dTpa	Pre	172	-	-	-	168	97.7	[94.2, 99.4]	59	[49, 70]
	Post	172	163	94.8	[90.3, 97.6]	172	100.0	[97.9, 100.0]	1019[1]	[897, 1157]
DTPa	Pre	83	-	-	-	82	98.8	[93.5, 100.0]	55	[44, 68]
	Post	83	83	100	[95.7, 100]	83	100.0	[95.7, 100.0]	1360[1]	[1159, 1595]

S+ = Titres ≥ 5 EU/ml
N = number of subjects tested in the specified cohort
n = number of subjects with a vaccine response or titres ≥ 5 EU/ml
95% CI = 95% confidence interval, lower and upper limit
[1] = a statistically significant difference between dTpa and DTPa groups (p<0.0167, 2-sided Wilcoxon test)
Vaccine response definition: For subjects seronegative at pre-vaccination: appearance of titre
For subjects seropositive at pre-vaccination: at least a two-fold increase
Calculated only for subjects with pre- and post-values available.

Table 2 Exact two-sided 90% CI for the treatment difference in anti-pertussis vaccine response rates and the two-sided 90% CI for the ratio of post-vaccination anti-pertussis GMTs between dTpa and DTPa groups - ATP Cohort for Immunogenicity Analysis

Group	Difference in proportion of vaccine responders (DTPa minus dTpa) [90% CI]	Ratio of GMT (DTPa/dTpa) [90% CI]
anti-PT		
DTPa versus dTpa	0.5 [-5.6 , 6.1]	1.24 [1.05, 1.47]
anti-FHA		
DTPa versus dTpa	7.7 [0.4 , 14.9]	1.13 [0.97, 1.31]
anti-PRN		
DTPa versus dTpa	5.2 [-0.7 , 11.5]	1.33 [1.12, 1.60] *

90% CI = two-sided 90% confidence interval, lower and upper limit
* = Since normality assumptions are not fulfilled, this confidence intervals might not be representative of the true treatment difference.

Document 1

Name of Company: SmithKline Biologicals, Rixensart, Belgium Name of Finished Product: Name of active substance: 208355/DTPa vaccine	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

Table 3 Anti-diphtheria and anti-tetanus antibody titres ≥0.1 IU/ml and GMTs - ATP Cohort for Immunogenicity Analysis

Group	Timing	N	≥0.1 IU/ml			GMT	
			n	%	95% CI	IU/ml	95% CI
Anti-diphtheria							
dTpa	Pre	171	145	84.8	[78.5, 89.8]	0.3	[0.3, 0.4]
	Post	172	172	100.0	[97.9, 100.0]	10.7[1]	[9.5, 12.1]
DTPa	Pre	82	70	85.4	[75.8, 92.2]	0.3	[0.2, 0.4]
	Post	83	83	100.0	[95.7, 100.0]	23.4[1]	[19.8, 27.8]
Td	Pre	81	70	86.4	[77.0, 93.0]	0.3	[0.3, 0.4]
	Post	81	81	100.0	[95.5, 100.0]	9.0	[7.4, 10.9]
Anti-tetanus							
dTpa	Pre	172	142	82.6	[76.0, 87.9]	0.3	[0.2, 0.3]
	Post	172	172	100.0	[97.9, 100.0]	13.4[2]	[11.8, 15.2]
DTPa	Pre	83	67	80.7	[70.6, 88.6]	0.2	[0.2, 0.3]
	Post	83	83	100.0	[95.7, 100.0]	11.4	[9.9, 13.2]
Td	Pre	81	65	80.2	[69.9, 88.3]	0.3	[0.2, 0.4]
	Post	81	81	100.0	[95.5, 100.0]	21.0[2]	[17.3, 25.6]

N = Number of subjects tested in the specified cohort n = number of subjects with titres within the specified range
% = percentage of subjects with titres within the specified range
95% CI = 95% confidence intervals, lower and upper limit
[1] = a statistically significant difference between dTpa and DTPa groups (p<0.0167, 2-sided Student's test)
[2] = a statistically significant difference between dTpa and Td groups (p<0.0167, 2-sided Wilcoxon test)

Table 4 Exact two-sided 90% CI for the treatment difference in proportion of subjects with post-vaccination anti-diphtheria and anti-tetanus titres ≥0.1 IU/ml and the two-sided 90% CI for the ratio of post-vaccination anti-diphtheria and anti-tetanus GMTs between dTpa and DTPa groups, and between dTpa and Td groups - ATP Cohort for Immunogenicity Analysis

Group	Difference in proportion* [90% CI] (DTPa minus dTpa or Td minus dTpa)	Ratio of GMT [90% CI] (DTPa/dTpa or Td/dTpa)
anti-diphtheria		
DTPa versus dTpa	0 [-5.8 , 3.3]	2.19 [1.84 , 2.61]
Td versus dTpa	0 [-6.0 , 3.3]	0.84 [0.70 , 1.01]†
anti-tetanus		
DTPa versus dTpa	0 [-5.8 , 3.3]	0.85 [0.72 , 1.01]†
Td versus dTpa	0 [-6.0 , 3.3]	1.57 [1.30 , 1.89]†

90% CI = 90% confidence intervals, lower and upper limit
* = Proportion of subjects with titres ≥ 0.1 IU/ml
† = Since normality assumptions are not fulfilled, these confidence intervals might not be representative of the true treatment difference.

Document 1

Name of Company: SmithKline Biologicals, Rixensart, Belgium Name of Finished Product: Name of active substance: 208355/DTPa vaccine	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

Reactogenicity (ATP cohort) (see Tables 5, 6 and 7)

- Pain was the most frequently reported solicited local symptom following administration of each of the vaccines and tended to occur more often after DTPa vaccination. Grade 3 pain was infrequent in all groups.
- The incidence of redness ≥50 mm tended to be similar following dTpa and Td vaccination and slightly higher following DTPa vaccination; the incidence of swelling ≥50 mm was similar in all groups.
- All solicited local symptoms had an onset on days 0, 1, or 2, although one case of pain and one case of redness became grade 3 and ≥50 mm, respectively, on day 3.
- Fever (axillary/oral temperature ≥37.5°C, rectal ≥38.0°C) was the most frequently reported solicited general symptom following administration of each of the vaccines. Fever ≥39.1°C (axillary/oral) or ≥39.6°C (rectal) assessed as probably or suspected to be related to vaccination was reported following between 1.1% and 2.2% of vaccinations in each group.
- Grade 3 solicited general symptoms assessed as probably or suspected to be related to vaccination were infrequent (none for diarrhoea, loss of appetite or vomiting, and one for irritability).
- Approximately 50% of solicited general symptoms had an onset on days 0, 1, or 2.
- The incidence of recurrent local and general symptoms (symptoms which occurred more than once with any two episodes being separated by at least one day with no symptoms) were similar for all groups: dTpa (12%), DTPa (12%) and Td (10%). The intensity, duration and timing of late-onset reactions were also similar for all groups.
- The incidence of symptoms with a late-onset was similar between dTpa (32%) and DTPa (29%) groups, while the incidence tended to be higher in the Td group (45%). The intensity, duration and timing of late-onset reactions were similar for all groups.
- One hundred and seventy-seven unsolicited symptoms, classified according to WHO preferred terms, (79 in the dTpa group, 54 in the DTPa group, 44 in the Td group) were reported by 130 subjects (60 in the dTpa group, 32 in the DTPa group, 38 in the Td group). The most common unsolicited adverse event was respiratory tract infection (16 subjects in the dTpa group, 16 subjects in the DTPa group and 14 subjects in the Td group). The most common unsolicited adverse event assessed by the investigator as probably related to the administration of the study vaccine was injection site reaction (8 subjects). None were assessed as suspected to be related. Only one unsolicited symptom was assessed as grade 3 (injection site reaction [pruritis] one day following administration of dTpa).
- Two serious adverse events were reported during the study:
  - Subject 20 was hospitalised 29 days after dTpa vaccination for a polypectomy (adenotomy). She recovered and was discharged from the hospital two days later. This event was assessed as not related to vaccination by the investigator.
  - Subject 151 burned his right hand 24 days after Td vaccination. The subject was subsequently hospitalised for skin transplantation. The child recovered with sequelae (scars). This event was assessed as not related to vaccination by the investigator.
- The parents of 22 subjects spontaneously contacted the investigator to report an extensive swelling. Twenty-one of these subjects had previously received four doses of DTPa (Infanrix™), while one subject had received three doses of DTPa as a primary vaccination and a reduced-dose formulation (1/5 DTPa) as a fourth dose. For the 21 subjects who had received four prior doses of DTPa, the incidence of these extensive swellings was similar following dTpa and Td vaccination. Of these 21 cases, 2 (both in the DTPa group) were reported to have involved shoulder-to-elbow swelling, and a further two cases (a case of chest swelling following DTPa vaccination, and a pronounced local reaction following dTpa vaccination) were notable. The swellings typically occurred on day 0 or day 1, were mild or moderate in intensity, involved an increase in arm circumference of about 3.8 cm, and lasted 4 days. All resolved spontaneously without sequelae.

No clear relationship between presence or absence of severe solicited adverse events after previous DTPa vaccination or severity of such adverse events, and the severity of adverse events following a fifth dose of dTpa, DTPa or Td vaccine was observed.

Name of Company: SmithKline Biologicals, Rixensart, Belgium Name of Finished Product: Name of active substance: 208355/DTPa vaccine	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

Table 5 The proportion of subjects with symptoms reported during the 15-day follow-up period was as follows (ATP cohort for reactogenicity analysis):

	dTpa (N=180)			DTPa (N=90)			Td (N=87)		
	n	%	[95% CI]	n	%	[95% CI]	n	%	[95% CI]
Any symptoms	133	73.9	[66.8, 80.1]	77	85.6	[76.6, 92.1]	69	79.3	[69.3, 87.3]
Local symptoms	106	58.9	[51.3, 66.2]	64	71.1	[60.6, 80.2]	57	65.5	[54.6, 75.4]
General symptoms	83	46.1	[38.7, 53.7]	49	54.4	[43.6, 65.0]	45	51.7	[40.8, 62.6]
Local solicited									
Pain Total	86	47.8	[40.3, 55.3]	57	63.3	[52.5, 73.2]	45	51.7	[40.8, 62.6]
Gr3	2	1.1	[0.1, 4.0]	2	2.2	[0.3, 7.8]	2	2.3	[0.3, 8.1]
Redness Total	61	33.9	[27.0, 41.3]	44	48.9	[38.2, 59.7]	32	36.8	[26.7, 47.8]
≥50 mm	24	13.3	[8.7, 19.2]	21	23.3	[15.1, 33.4]	15	17.2	[10.0, 26.8]
Swelling Total	58	32.2	[25.5, 39.6]	39	43.3	[32.9, 54.2]	30	34.5	[24.6, 45.4]
≥50mm	24	13.3	[8.7, 19.2]	14	15.6	[8.8, 24.7]	12	13.8	[7.3, 22.9]
General solicited									
Diarrhoea	18	10.0	[6.0, 15.3]	8	8.9	[3.9, 16.8]	11	12.6	[6.5, 21.5]
Irritability	29	16.1	[11.1, 22.3]	19	21.1	[13.2, 31.0]	19	21.8	[13.7, 32.0]
Loss of appetite	32	17.8	[12.5, 24.2]	16	17.8	[10.5, 27.3]	18	20.7	[12.7, 30.7]
Fever* ≥37.5°C	36	20.0	[14.4, 26.6]	20	22.2	[14.1, 32.2]	28	32.2	[22.6, 43.1]
≥39.1°C	10	5.6	[2.7, 10.0]	4	4.4	[1.2, 11.0]	4	4.6	[1.3, 11.4]
Vomiting	14	7.8	[4.3, 12.7]	4	4.4	[1.2, 11.0]	4	4.6	[1.3, 11.4]

N = number of documented doses
n = number of doses followed by the particular symptom
% = percentage of symptoms reported
Gr 3 = grade 3 = Adverse experience which prevented normal everyday activities and need medical advice
* Fever = axillary/oral temperature ≥37.5°C, rectal ≥38.0°C; Grade 3 fever = axillary/oral temperature ≥39.1°C, rectal ≥39.6°C
95% CI = 95% confidence intervals, lower and upper limit

Table 6 The exact two-sided 90% CI for the difference between dTpa and Td/DTPa groups for adverse events (ATP cohort for reactogenicity analysis)

	Difference in proportion: DTPa minus dTpa (%)	[90% CI]	Difference in proportion: Td minus dTpa (%)	[90% CI]
No adverse experience	-11.7	[-20.9, -1.6]	-5.4	[-15.6, 5.0]
Local symptom	12.2	[1.3, 23.2]	6.6	[-4.2, 18.3]
General symptom	8.3	[-2.6, 19.7]	5.6	[-5.3, 17.5]
Pain	15.6	[4.6, 26.8]	3.9	[-7.0, 15.9]
Redness	15.0	[4.1, 26.2]	2.9	[-7.7, 14.8]
Swelling	11.1	[0.2, 22.4]	2.3	[-8.3, 14.2]
Fever	2.2	[-7.5, 13.1]	12.2	[2.0, 23.8]

90% CI = exact 90% confidence intervals, lower and upper limit

Document 1

Name of Company: SmithKline Biologicals, Rixensart, Belgium Name of Finished Product: Name of active substance: 208355/DTPa vaccine	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

Table 7 Extensive swellings (ITT cohort for reactogenicity) (Analysis for the 21 subjects receiving four prior doses of DTPa)

	dTpa (N = 211)	DTPa (N = 107)	Td (N = 103)
Swelling	**n (%)**	**n (%)**	**n (%)**
Reported to investigator	7 (3.3)	9 (8.4)	5 (4.9)
Shoulder-to-elbow	0	2 (1.9)	0
Notable	1 (0.5)	1 (0.9)	0

N = Number of subjects
n = Number of subjects with a report of the symptom
% = Percentage of subjects with a report of the symptom

Conclusions:

- dTpa and DTPa vaccines were both highly immunogenic for pertussis antigens. Both vaccines induced a similar immune response to the pertussis components.
- All vaccines were highly immunogenic for diphtheria and tetanus: all but 3 subjects for both anti-diphtheria and anti-tetanus had post-vaccination titres ≥1.0 IU/ml (a value approximately 100 times the protective titre). GMTs were high. dTpa was similarly immunogenic to the Td vaccine in terms of post-vaccination anti-diphtheria titres, while DTPa induced higher titres. dTpa and DTPa induced similar anti-tetanus titres, while Td induced higher titres. The clinical relevance of differences in titres is unknown in view of the fact that nearly all subjects had titres ≥1.0 IU/ml.
- The dTpa, DTPa and Td vaccines were shown to be safe and well tolerated when administered as a single booster dose to children 4 to 6 years of age who had previously received 4 doses of DTPa (Infanrix™). Although the incidences of some adverse experiences, notably pain, were high, the incidences of grade 3 adverse experiences were low. Solicited local symptoms (pain, redness and swelling) occurred with a similar incidence following dTpa and Td vaccination, while tending to occur with more often after DTPa vaccination.
- Prior to vaccination, almost all subjects (from the dTpa and DTPa groups) were seropositive for anti-FHA and anti-PRN antibodies, approximately half were seropositive for anti-PT antibodies and more than 80% (from all groups) had anti-tetanus and anti-diphtheria titres ≥ 0.1 IU/ml.

Date of report: October 15, 1998

Document 1

Name of Company: SmithKline Beecham Biologicals, Rixensart, Belgium **Name of Finished Product:** Infanrix® **Name of active substance:** 208355/DTPa vaccine	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Title of the study : 208355/120 (APV-120)
Clinical study of the reactogenicity and immunogenicity of SB Biologicals' DTPa vaccine administered as a booster to healthy children 4 to 6 years of age, previously vaccinated with four doses of SB Biologicals' DTPa vaccine in the first two years of life.

Principal Investigator : s22 [redacted]

Study centre: Kinderklinik, Johannes-Gutenberg-Universität
Langenbeckstraße 1
55101 Mainz, Germany

Publication (reference): None, as of January 20, 1999

Study period: Started: October 2, 1997
Ended: September 8, 1998

Clinical phase: III

Objectives:
The primary objective of the study APV-120 was:
- To evaluate the reactogenicity of the study vaccine.

The secondary objectives were:
- To assess the immunogenicity of a fifth dose of SB Biologicals' DTPa vaccine, in terms of the humoral immune response to the three pertussis antigens [pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN)], one month after the fifth dose.
- To assess the immunogenicity of SB Biologicals' DTPa vaccine in terms of the humoral immune response to the diphtheria and tetanus toxoids, one month after the fifth dose.
- To evaluate the persistence of antibodies to the three pertussis antigens, diphtheria and tetanus, immediately prior to the fifth dose.

Methodology:
Design: Open, uncontrolled, non-randomised, single-centre, multi-site booster study
Population group: Healthy children, between 4 and 6 years of age, previously vaccinated with four doses of SB Biologicals' DTPa vaccine in the first 2 years of life.

Number of subjects (total and for each treatment):
Enrolled: 413; Completed: 410
ITT analysis for safety: 410; ITT analysis for immunogenicity: 145
ATP analysis for safety: 379; ATP analysis for immunogenicity: 126

Diagnosis and criteria for inclusion:
- Subjects must have been vaccinated with four doses of SB Biologicals' DTPa vaccine in their first two years of life.
- Subjects must have been healthy and between 4 and 6 years of age at the time of vaccination.
- Written informed consent must have been obtained from the parents/guardians of the subject.

Test Vaccine, dose, mode of administration, batch no.:
SB Biologicals' combined **DTPa vaccine**, containing per 0.5 ml dose: ≥30 IU (25 Lf) diphtheria toxoid; ≥40 IU (10 Lf) tetanus toxoid; 25 mcg PT; 25 mcg FHA; 8 mcg PRN; 0.5 mg Aluminum salts; 2.5 mg Phenoxyethanol. Lot DTPa833A2/M
Route: Intramuscular injection in the left deltoid region.

Document 1

Name of Company: SmithKline Beecham Biologicals, Rixensart, Belgium **Name of Finished Product:** Infanrix® **Name of active substance:** 208355/DTPa vaccine	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Criteria for evaluation:

Reactogenicity: Incidence of any symptoms, local and general symptoms, after vaccination, in addition to occurrence of each individual local solicited symptom by onset (with intensity), general solicited symptoms by onset (with intensity and relationship), and unsolicited symptoms (with intensity and relationship), and serious adverse events. Follow-up period for solicited symptoms was days 0-14, for unsolicited symptoms and for serious adverse events, days 0-30. An additional page in the CRF was provided in order to collect data on extensive swelling.

Immunogenicity: Determination of the antibody titres against pertussis antigens (PT, FHA and PRN), diphtheria and tetanus toxoids, prior to and one month after vaccination.

Serum antibody titres against pertussis antigens were determined by ELISA with a cut-off of 5 EU/ml. A vaccine response to the pertussis antigens was defined as the appearance of an antibody titre ≥ cut-off in initially seronegative subjects, or as at least a two-fold increase of a positive pre-vaccination titre. Antibodies to diphtheria and tetanus toxoids were measured by ELISA with a cut-off of 0.1 IU/ml. Anti-diphtheria titres < cut-off of ELISA were re-tested by the more sensitive VERO test with a cut-off of 0.016 IU/ml. For GMT (geometric mean of titres) calculations, antibody titres below the cut-off of the assay were given an arbitrary value of half the cut-off.

Statistical methods:

Immunogenicity: The seropositivity rates/vaccine response rates one month after vaccination and their 95% CIs were calculated; antibody titres were summarised by GMTs, their 95% CIs and reverse cumulative distribution curves.

Reactogenicity: The percentage of subjects reporting symptoms within the 15 days following vaccination and their 95% confidence intervals (CIs) were computed. The incidence of solicited symptoms (swelling, redness and fever) during the 15-day follow-up period was summarised using reverse cumulative distribution curves.

Summary: Results

Reactogenicity (ATP Cohort): See Tables 1, 2 and 3 in synopsis

Solicited local symptoms:

- Each solicited local symptom was reported with similar frequency (approximately 50%) following vaccination.
- Redness ≥50 mm was more frequently reported than swelling ≥50 mm. Reports of pain graded 3 were rare.
- All solicited local symptoms had onset on days 0, 1 or 2, except for 3 cases of pain and swelling and 1 case of redness.

Extensive swelling:

- Information on spontaneous reports of extensive swelling (according to parents' judgment) were recorded on an additional page of the CRF. This CRF page detailed the start date, the end date, the circumference, the intensity, pain and warmth of the swelling, associated redness, in addition to the subjects body temperature (6.3% of the subjects enrolled in the study had such a report). In some cases the investigator described the extensive swelling in more detail; these cases were considered as "notable" (notable swelling was reported at a frequency of only 0.5% [2 of 410 subjects]).

Name of Company: SmithKline Beecham Biologicals, Rixensart, Belgium Name of Finished Product: Infanrix® Name of active substance: 208355/DTPa vaccine	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

- Of the 413 enrolled subjects (total cohort), the parents of 26 subjects spontaneously contacted the investigator to report extensive swelling. All subjects in whom extensive swelling was reported were vaccinated in the left deltoid muscle, according to protocol. The majority of cases of reporting extensive swelling were clustered at 3 study sites: site 502, site 214 and site 422.
- The profile of the swelling in terms of incidence, diameter, circumference of the injected arm, duration and intensity was as follows: The mean diameter of the swelling was 102 mm (range 0 - 250 mm), and the mean increase in circumference of the injected arm was 39 mm (range: 12 - 160 mm). The swelling had an onset within three days of booster dose administration in all subjects. The median swelling duration (including start date and end date) was 4 days (range: 1-10 days). All cases of extensive swelling (except 1) were assessed as grade 1 or 2 in intensity and most were associated with local or diffuse redness (26 of 26 cases), local or diffuse warmth (21of 26 cases) and local or diffuse pain (23 of 26 cases).
- Of the 26 reports of extensive swelling, two cases were regarded as notable by the principal investigator (frequency : 0.48% of total subjects included in the ITT analysis of safety).

Solicited general symptoms:

- Fever (axillary/oral temperature ≥37.5°C [99.5°F] or rectal temperature ≥38.0°C [100.4°F]) was the most frequently reported solicited general symptom following vaccination. Fever ≥39.1°C [102.4°F] (axillary/oral) or≥39.6°C [103.3°F] (rectal) assessed as 'probable' or 'suspected' to be related to vaccination was reported following 0.8% of vaccinations.
- Grade 3 solicited general symptoms assessed as 'probable' or 'suspected' to be related to vaccination were infrequent (none for vomiting, 1 each for diarrhoea, irritability and loss of appetite and 3 for fever). Approximately 50% of solicited general symptoms had an onset on days 0, 1 or 2.

Document 1

Name of Company: SmithKline Beecham Biologicals, Rixensart, Belgium **Name of Finished Product:** Infanrix® **Name of active substance:** 208355/DTPa vaccine	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Table 1: The proportion of subjects with symptoms reported during the 15-day follow-up period after vaccination was as follows (ATP Cohort for Safety Analysis):

Symptom	Intensity	N = 376		
		n	%	95%CI
Any	All	302	80.3	[75.9, 84.2]
Any General		191	50.8	[45.6, 56.0]
Any Local		249	66.2	[61.2, 71.0]
Pain	All	192	51.1	[45.9, 56.2]
	Grade 3	6	1.6	[0.6, 3.4]
Redness	All	197	52.4	[47.2, 57.5]
	≥ 50 mm	114	30.3	[25.7, 35.2]
Local Swelling	All	194	51.6	[46.4, 56.8]
	≥ 50 mm	80	21.3	[17.2, 25.8]
Diarrhoea	Total	39	10.4	[7.5, 13.9]
	Grade 3	1	0.3	[0.0, 1.5]
Irritability	Total	64	17.0	[13.4, 21.2]
	Grade 3	1	0.3	[0.0, 1.5]
Loss of appetite	Total	66	17.6	[13.8, 21.8]
	Grade 3	4	1.1	[0.3, 2.7]
Fever	Total*	94	25.0	[20.7, 29.7]
	Grade 3**	9	2.4	[1.1, 4.5]
Vomiting	Total	29	7.7	[5.2, 10.9]
	Grade 3	2	0.5	[0.1, 1.9]

N = number of documented doses (= doses for which a symptom sheet was completed)
n = number of documented doses followed by the particular symptom
% = percentage of symptoms reported
Grade 3 = adverse experience which prevented normal everyday activities and necessitated medical advice
* Fever = axillary/oral temperature ≥ 37.5°C; rectal temperature temperature ≥ 38.0°C
**Grade 3 fever = axillary/oral temperature ≥ 39.1°C; rectal temperature ≥ 39.6°C
95% CI = 95% confidence intervals, lower and upper limit

Synopsis of final study report APV-120 (208355/120) – page 4 of 7

Doc ID

Name of Company: SmithKline Beecham Biologicals, Rixensart, Belgium **Name of Finished Product:** Infanrix® **Name of active substance:** 208355/DTPa vaccine	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Table 2: Characteristics of extensive swellings (ITT Cohort for Safety Analysis) (Analysis for the 26 subjects receiving four prior doses of DTPa)

Characteristics	Statistics or Categories	N = 410
Total reports of extensive swelling		26 (6.3%)
Intensity*	Grade 1	14
(n)	Grade 2	11
	Grade 3	1
Day of onset	Minimum	0
	Median	1
	Maximum	2
Duration	Minimum	1
(days)	Median	4
	Maximum	10
Diameter†	Minimum	0
(mm)	Mean	102
	Maximum	250
Increase in circumference ‡	Missing value	3
(mm)	Minimum	12
	Median	30
	Mean	39
	Maximum	160

N = number of documented doses
n = number of subjects with specified intensity of extensive swelling
* Intensity of extensive swelling was graded as follows:
Grade 1 = adverse experience which was easily tolerated.
Grade 2 = adverse experience which caused sufficient discomfort to interfere with daily activities
Grade 3 = adverse experience which prevented normal everyday activities and necessitated medical advice
† maximum diameter, in mm, of local swelling reported during the 15-day follow-up period (from the symptom sheet).
‡ Increase in circumference of injected limb as compared to unaffected limb.

Table 3: Extensive swelling (ITT Cohort for Safety Analysis)

Extensive Swelling	Fifth dose DTPa (N= 410) n (%)
Reported to Investigator	26 (6.3%)
Notable	2 (0.5%)
- Shoulder-to-elbow	1 (0.2%)

N= number of subjects included in the ITT analysis of safety
n = number of subjects reporting specified extensive swelling
% = percent of subjects reporting specified extensive swelling

Name of Company: SmithKline Beecham Biologicals, Rixensart, Belgium **Name of Finished Product:** Infanrix® **Name of active substance:** 208355/DTPa vaccine	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Unsolicited signs and symptoms:

- Two hundred and twenty unsolicited symptoms classified according to WHO preferred terms were reported by 143 subjects. The most common unsolicited adverse event was upper respiratory tract infection and pruritus (21 cases each, ATP cohort). The most common unsolicited adverse event assessed by the investigator as 'probable' or 'suspected' to be related to the administration of the study vaccine was pruritus (21 cases, ATP cohort). Three (1.4%) unsolicited symptoms were assessed by the investigator as intensity grade 3:

Subjects n°76 and n°82 experienced an injection site reaction (pruritus) on the day of vaccination, which resolved within one day and was assessed as 'probably related' to vaccination; and subject n°297 developed a viral infection, 14 days after vaccination and the subject recovered after 4 days. The symptom was assessed as 'not related' to vaccination by the investigator.

ious adverse events:

- No serious adverse events were reported during the course of the study.

Immunogenicity (ATP Cohort): See Tables 4 and 5 of synopsis

- Pre-vaccination, the majority of subjects (78.6-99.2%) were seropositive for antibodies to FHA, PRN and tetanus and diphtheria toxoids, and approximately 37% were seropositive for anti-PT antibodies.
- Most subjects in the ATP cohort had a vaccine response to PT (98.4%), FHA (93.7%) and PRN (99.2%).
- Post-vaccination, all subjects had anti-diphtheria and anti-tetanus antibodies ≥1.0 IU/ml.
- With regard to GMTs, there was an increase of 16.2-fold for anti-PT, 11.2-fold for anti-FHA and 22-fold for anti-PRN, 81-fold for anti-diphtheria antibodies and approximately 37-fold for anti-tetanus antibodies.

Table 4: Vaccine response rates, seropositivity rates and geometric mean titres (GMTs) for anti-PT, anti-FHA and anti-PRN antibodies - ATP Cohort for Immunogenicity Analysis

Timing	N	VR			S+			GMT	(EU/ml)
		n	%	[95% CI]	n	%	[95% CI]	Value	[95%CI]
Anti-PT									
Pre	126	-	-	-	47	37.3	[28.9, 46.4]	4.2	[3.6, 4.8]
Post	126	124	98.4	[94.4, 99.8]	126	100.0	[97.1, 100.0]	68.2	[59.4, 78.3]
Anti-FHA									
Pre	126	-	-	-	125	99.2	[95.7, 100.0]	68.6	[54.7, 86.1]
Post	126	118	93.7	[87.9, 97.2]	125	100.0	[97.1, 100.0]	770.6	[682.0, 870.7]
Anti-PRN									
Pre	126	-	-	-	124	98.4	[94.4, 99.8]	58.2	[47.5, 71.2]
Post	126	125	99.2	[95.7, 100.0]	126	100.0	[97.1, 100.0]	1274.8	[1104.2, 1471.8]

S+ = Titres≥ 5 EU/ml
N = number of subjects tested in the specified cohort
n = number of subjects with a vaccine response or titres ≥ 5 EU/ml
95% CI = 95% confidence interval, lower and upper limit
Vaccine response definition: For subjects seronegative at pre-vaccination: appearance of titre
For subjects seropositive at pre-vaccination: at least a two-fold increase
Calculated only for subjects with pre- and post-values available

Synopsis of final study report APV-120 (208355/120) – page 6 of 7

Name of Company: SmithKline Beecham Biologicals, Rixensart, Belgium **Name of Finished Product:** Infanrix® **Name of active substance:** 208355/DTPa vaccine	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Table 5: Seropositivity rates and GMTs for anti-diphtheria and anti-tetanus antibodies - ATP Cohort for Immunogenicity Analysis

Timing	N	S+ n	S+ %	S+ 95%CI	GMT IU/ml	GMT 95% CI
Anti-diphtheria						
Pre	124	107	86.3	[79.0, 91.8]	0.249	[0.208, 0.299]
Post	126	126	100.0	97.1, 100.0]	20.195	[17.444, 23.381]
Anti-tetanus						
Pre	126	99	78.6	[70.4, 85.4]	0.268	[0.218, 0.33]
Post	126	126	100.0	[97.1, 100.0]	10.157	[9.009, 11.452]

N = Number of subjects tested in the specified cohort
S+ = seropositive i.e. with titres ≥0.1 IU/ml
n = number of subjects with titres within the specified range
% = percentage of subjects with titres ≥0.1 IU/ml
95% CI = 95% confidence intervals, lower and upper limit

Conclusions:

- The DTPa vaccine was shown to be safe and the reactogenicity acceptable when administered as a fifth dose to children 4 to 6 years of age who had previously received 4 doses of DTPa (Infanrix®). The vaccination frequently induced mild or moderate local reactions (pain [51.1%], local swelling [51.6%], redness [52.4%]). However, the incidences of grade 3 pain, and grade 3 solicited general symptoms were low.
- Extensive swelling (according to the parents judgment) was reported at a frequency of 6.3%; however, notable swellings were reported at a frequency of only 0.5% (2 of 410 subjects).
- The DTPa vaccine was highly immunogenic as a fifth dose for pertussis antigens and induced ≥93.7% immune response to each of the pertussis components. The vaccine was also highly immunogenic for diphtheria and tetanus: all subjects had anti-diphtheria and anti-tetanus post-vaccination titres ≥1.0 IU/ml (a value approximately 100 times the protective titre).
- Prior to vaccination, the majority of subjects (78.6-99.2%) were seropositive for antibodies to FHA, PRN and tetanus and diphtheria toxoids and approximately 37% were seropositive for anti-PT antibodies.
- The results of this study are consistent with the results of controlled study APV-118. In study APV-118, one group (n =107) received DTPa as a fifth dose. The reactogenicity and immunogenicity results observed in this group were similar to those observed in the present study.

Date of report: February 2,1999.

Synopsis of final study report APV-120 (208355/120) – page 7 of 7

Document 1

Name of company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of finished product:** **Name of active substance:** DTPa-IPV/Hib	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Title of the study: Double blind clinical study to assess the immunogenicity and reactogenicity of a booster dose of GlaxoSmithKline Biologicals' Hib vaccine conjugated with one of two tetanus toxoid carriers administered mixed as single injection with GSK Biologicals' DTPa-IPV vaccine at 17 to 19 months of age in infants primed in the study DTPa-IPV-039

Principal Investigators: s22 and s22

Study Center(s): Multiple study sites in Lithuania

Publication (reference): None as of September 2001

Study period:	**Clinical phase:** III
Date of first visit: 30 December 1999 Date of last visit: 4 May 2000	

Objectives

Primary

To demonstrate, in terms of immunogenicity of the PRP antigen, that the Hib vaccine conjugated with tetanus toxoid supplied by Human Co. (Hib-TH) is equivalent to Hib conjugated with tetanus toxoid supplied by Chiron-Behring (Hib-TB) when mixed extemporaneously with the DTPa-IPV vaccine and given in a single injection as a booster dose.

Secondary

- To demonstrate equivalence in terms of immunogenicity of all other vaccine antigens (diphtheria toxoid, tetanus toxoid, the three pertussis antigens [PT, FHA and PRN], and the three polio antigens) between the Hib-TH and Hib-TB vaccine groups when mixed extemporaneously with the DTPa-IPV vaccine and given in a single injection as a booster dose.
- To assess the reactogenicity and safety of the study vaccines in both groups.
- To assess the antibody persistence of all vaccine antigens (PRP, diphtheria toxoid, tetanus toxoid, the three pertussis antigens [PT, FHA and PRN], and the three polio antigens), just before the booster dose in both groups.

Methodology:

Study design: Double-blind, randomised, controlled, multi-site booster study (7 sites) with 2 groups in a balanced allocation (1:1).

- Group 1 received DTPa-IPV vaccine mixed with Hib-TH vaccine (subjects were randomly selected from the cohort primed in study DTPa-IPV-039 with the same vaccine)
- Group 2 received DTPa-IPV vaccine mixed with Hib-TB vaccine (subjects were randomly selected from the cohort primed in study DTPa-IPV-039 with the same vaccine)

Blood samples were taken immediately before the booster dose and one month after the booster.
All subjects received their booster dose between 30 December 1999 and 20 March 2000.

Number of subjects:

Planned: 200 (100 per group)
Enrolled (Total cohort): 200 (102 in group 1and 98 in group 2)
Completed: 196 (98 per group)
According to protocol (ATP) cohort for immunogenicity analysis: 190 (94 in group 1 and 96 in group 2)
ATP cohort for safety analysis: 199 (101 in group 1 and 98 in group 2).

Name of company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of finished product:** **Name of active substance:** DTPa-IPV/Hib	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Diagnosis and criteria for inclusion:
Healthy male and female infants between 17 and 19 months of age, free of obvious health problems. Subject's parent(s)/guardian(s) must have provided written informed consent. Subjects previously completed a 3-dose primary vaccination course of DTPa-IPV and Hib in study DTPa-IPV-039.

Test product, dose, site of administration, lot no.:

Vaccines:

- GSK Biologicals' liquid combined **DTPa-IPV vaccine** containing per 0.5 ml dose: ≥ 30 IU (25 Lf) Diphtheria toxoid, ≥ 40 IU (10 Lf) Tetanus toxoid, 25 µg pertussis toxoid (PT), 25 µg filamentous haemaglutinin (FHA), 8 µg pertactin (PRN), 40D antigen units Polio virus type 1 (Mahoney strain), 8D antigen units Polio virus type 2 (MEF-1 strain), 32D antigen units Polio virus type 3 (Saukett strain), 0.5 mg aluminium (as salts) and 2.5 mg phenoxyethanol. Lot number D20751A2 was used in each group.
- GSK Biologicals' lyophilized ***Haemophilus influenzae*** **type b** conjugate vaccine containing per 0.5 ml dose: 10 µg Polyribosyl-Ribitol-Phosphate (PRP), 20-40 µg Tetanus toxoid, 10 mg Lactose. GSK Biological's Hib conjugate vaccine conjugated with tetanus toxoid from Human Co. (Hib-TH), lot number Hib605A47.

GSK Biologicals' DTPa-IPV vaccine and Hib-TH (or Hib-TB reference vaccine [see below]) were combined in one injection and administered intramuscularly in the right anterolateral thigh.

Reference therapy, dose, lot no.:

Vaccine: GSK Biologicals' Hib vaccine conjugated with tetanus toxoid from Chiron-Behring GmbH (Hib-TB), lot number Hib237A41.

Duration of treatment: Approximately 1 month.

Criteria for evaluation:

Immunogenicity:

Measurement of antibody titres against each vaccine antigen, prior to the booster dose and one month after the booster dose.

The primary endpoint was anti-PRP antibody titres one month after the booster dose.

The secondary endpoints included:

- for each blood sampling time point, antibody titres for anti-polio types 1, 2 and 3, anti-PT, anti-FHA, anti-PRN, anti-diphtheria and anti-tetanus antibodies, anti-PRP antibody titer ≥ 1.0 µg/ml and ≥ 0.15 µg/ml, anti-polio types 1, 2 and 3 antibody titers ≥ 8 and anti-diphtheria and anti-tetanus antibody titer ≥ 0.1 IU/ml.
- one month after the booster dose of the study vaccines, vaccine response to PT, FHA and PRN. Vaccine response rates for PT, FHA and PRN are defined as the appearance of antibodies (titre ≥ 5 EL.U/ml) in subjects who are initially seronegative, or at least a two-fold increase in antibody titres from pre to post-vaccination in subjects who are initially seropositive.

Note that for the analysis of pre-booster antibody persistence, data were pooled with the results from study DTPa-HAV-IPV-001, another booster study enrolling subjects at 17 to 20 months of age following priming in study DTPa-IPV-039.

Document 1

Name of company: GlaxoSmithKline Biologicals, Rixensart, Belgium Name of finished product: Name of active substance: DTPa-IPV/Hib	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

Safety and Reactogenicity:
Safety and reactogenicity data were collected for all subjects and included: recording of solicited local and general adverse events by the parents/guardians during a four-day follow-up period after the booster dose; recording of unsolicited adverse events occurring within 30 days after vaccination and recording of all serious adverse events (SAE's) occurring during the study period.

Statistical methods:
All analyses/summaries were performed using SAS 6.12 and StatXact 3.0 on Windows.

Immunogenicity

Demonstration of equivalence between vaccines when given as a booster:
The exact two-sided 90% CIs for treatment difference in seroprotection rate or vaccine response rate between DTPa-IPV/Hib-TB and DTPa-IPV/Hib-TH groups were computed. For anti-PRP, anti-PT, anti-FHA and anti-PRN, the 90% CIs for the ratio of post-booster GMTs between DTPa-IPV/Hib-TB and DTPa-IPV/Hib-TH groups were computed using a one-way ANOVA model on the $\log_{10}$ transformation of the titres.

If the confidence interval pertaining to an antigen was within the following clinical limits defining equivalence, the DTPa-IPV/Hib-TB and DTPa-IPV/Hib-TH groups were deemed equivalent with respect to that particular antigen (2-fold difference [0.5, 2] for anti-PRP GMT and anti-PT, FHA and PRN GMTs, 10% difference [-10%, +10%] for anti-PRP $\geq$ 1.0 µg/mL, anti-diphtheria and anti- tetanus $\geq$ 0.1 IU/mL, anti-polio types 1, 2 and 3 $\geq$ 8 and anti-PT, FHA and PRN vaccine response).
The primary comparison focused on anti-PRP antibody titres.

Safety and Reactogenicity:

The percentage of subjects reporting symptoms during the 4-day follow-up period after the booster dose were reported with 95% CIs. The percentage of subjects with unsolicited AEs occurring within 30 days after booster vaccination were tabulated. SAE's were described.
Statistical comparisons were exploratory. Differences between groups for proportions of subjects reporting any AE, any general AE and any local AE during the 4-day follow-up period were evaluated using 90% CIs.

SUMMARY and CONCLUSIONS
Demography: The groups were similar in terms of age and gender.

Immunogenicity results:

Antibody persistence
Data collected for 199 subjects (101 and 98 in the Hib-TH and Hib-TB groups, respectively) from this DTPa-IPV-043 booster study and for 489 subjects (419 and 70 in the Hib-TH and Hib-TB groups, respectively) from study DTPa-HAV-IPV-001 were included in the ATP cohort for persistence.

- Antibody persistence measured approximately 11 months after the third dose of the 3-dose primary vaccination course was similar between groups.

Name of company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of finished product:** **Name of active substance:** DTPa-IPV/Hib	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

- Anti-PRP antibody persistence remained high (94.8% and 93.5% of subjects who received DTPa-IPV/HibTH or DTPa-IPV/Hib-TB respectively had titres ≥ 0.15 µg/ml) approximately 11 months after the third dose of the primary vaccination course.
- At least 35% of subjects in each group still had protective anti-diphtheria antibody titre levels by ELISA (≥0.1 IU/ml), and most subjects enrolled in this booster study (> 95% in the ATP cohort for immunogenicity), still had neutralising antibodies by Vero-veil assay (≥0.016 IU/ml).
- At least 72% of subjects per group still had protective anti-tetanus antibody titres (≥0.1IU/ml).

- At least 95.7% of subjects still had protective anti-polio types 1, 2 and 3 titres (≥ 8) approximately 11 months after the third dose of the primary vaccination.
- At least 62.3% of subjects per group were still seropositive (≥5 EL.U/ml) for anti-PT antibodies, 98.6% for anti-FHA antibodies and 85.3% for anti-PRN antibodies approximately 11 months after the third dose of the primary vaccination course.

Post-booster immunogenicity –equivalence of groups

Table 1 presents the GMT ratios between groups with 90% CIs (ATP cohort).

Table 1: GMT ratios one month after the booster dose (ATP cohort for immunogenicity)

Antibody	Group 1		Group 2		Ratio of GMT (Group 1 divided by group 2)		
	N	GMT	N	GMT	value	90% CI	
Anti-PRP	94	120.620	96	79.496	1.517	1.171	1.966*
Anti-diphtheria	94	3.857	96	3.657	1.055	0.862	1.291†
Anti-tetanus	94	6.311	96	5.202	1.213	1.013	1.453†
Anti-polio type 1	85	1667.2	85	1745.1	0.955	0.751	1.215†
Anti-polio type 2	55	1630.3	60	1531.7	1.064	0.823	1.376†
Anti-polio type 3	57	2107.6	61	2201.0	0.958	0.723	1.268†
Anti-PT	94	162.7	96	169.2	0.962	0.793	1.167*
Anti-FHA	94	538.9	96	550.1	0.980	0.834	1.151*
Anti-PRN	94	573.0	96	616.2	0.930	0.741	1.167*

Group 1: DTPa-IPV mixed with Hib-TH
Group 2 : DTPa-IPV mixed with Hib-TB
N = number of subjects with available results
90% CI = 90% confidence intervals
* = Within the pre-defined clinical limit for equivalence (2-fold difference [0.5, 2]) for anti-PRP GMT and anti-PT, FHA and PRN GMTs
† = These results are exploratory, i.e., no clinical limits for equivalence were defined

The two Hib vaccine formulations TH and TB, mixed with DTPa-IPV were equivalent in terms of antibody titres to PRP, PT, FHA and PRN.

Table 2 presents the seroprotection/vaccine response rates one month after the booster dose and the difference between groups with 90% CIs.

Document 1

Name of company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of finished product:** **Name of active substance:** DTPa-IPV/Hib	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Table 2: Differences in seroprotection/vaccine response rates one month after the booster dose (ATP cohort for immunogenicity)

Antibody	Group 1		Group 2		Difference (Group 1 minus group 2)		
	N	Rate (%)	N	Rate(%)	Value(%)	90% CI	
Anti-PRP ≥ 0.15 µg/ml	94	100	96	100	0	-5.6	5.4†
Anti-PRP ≥ 1.0 µg/ml	94	100	96	100	0	-5.6	5.4*
Anti-Diphtheria ≥ 0.1 IU/ml	94	100	96	100	0	-5.6	5.4*
Anti-Tetanus ≥ 0.1 IU/ml	94	100	96	100	0	-5.6	5.4*
Anti-Polio 1 ≥ 8	85	100	85	100	0	-6.1	6.1*
Anti-Polio 2 ≥ 8	55	100	60	100	0	-9.6	8.2*
Anti-Polio 3 ≥ 8	57	100	61	100	0	-9.2	8.2*
Vaccine response to PT	94	97.9	95	100	-2.1	-8.9	3.8*
Vaccine response to FHA	92	94.6	94	97.9	-3.3	-11.6	4.3
Vaccine response to PRN	94	97.9	95	96.8	1.0	-5.5	9.3*

Group 1: DTPa-IPV mixed with Hib-TH
Group 2 : DTPa-IPV mixed with Hib-TB
N = number of subjects with available results
† = These results are exploratory, i.e., no clinical limits for equivalence were defined
* Within the pre-defined clinical limit for equivalence (−10%, +10%) for anti-PRP>1.0ug/ml, anti-diphtheria, anti-tetanus, anti-polio types 1, 2 and 3 seroprotection rates and vaccine response to anti-PT and PRN antibodies
90% CI = Exact 90% confidence intervals
Vaccine response: titre ≥ cut-off 5 EL.U/ml for initially seronegative subjects or at least a two-fold increase in antibody titres from pre-vaccination to post-vaccination in subjects who were initially seropositive.

Results show equivalence of Hib-TH mixed with DTPa-IPV vaccine versus Hib-TB mixed with DTPa-IPV vaccine for the percentage of subjects who had protective levels for anti-PRP, anti-diphtheria, anti-tetanus, anti-polio 1, 2 and 3 and vaccine responses to PT and PRN; for all these parameters, the limits of the 90% CI of treatment difference were within the corresponding clinical limit for equivalence. For anti-FHA vaccine response, although the absolute difference between the 2 groups did not exceed 10%, the greatest 90% CI limit on treatment differences (11.6%) marginally exceeded the *a priori* defined 10% clinical limit for equivalence.

Safety and reactogenicity results

Differences between groups with regard to the percentage of subjects reporting symptoms, both solicited and unsolicited during the 4-day follow-up period following the booster dose, with 90% CI are presented in Table 3. These results are considered exploratory.

Name of company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of finished product:** **Name of active substance:** DTPa-IPV/Hib	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Table 3: Differences between groups in the percentage of subjects reporting solicited and unsolicited symptoms during the 4-day follow-up period following the booster dose (ATP cohort for reactogenicity)

Percentage of subjects	Group 1 N=101		Group 2 N=98		Difference (Group 1 minus Group 2)		
experiencing:	n	%	n	%	Value (%)	90%CI	
Any symptom	86	85.1	89	90.8	-5.7	-16.3	3.6
Any general symptom	67	66.3	65	66.3	0	-11.8	12.4
Any local symptom	72	71.3	79	80.6	-9.3	-21.4	1.6

Group 1: DTPa-IPV mixed with Hib-TH
Group 2 : DTPa-IPV mixed with Hib-TB
N = number of subjects with a documented dose
n= number of subjects with a particular type of symptom
% = percentage of subjects reporting a specified symptom
90% CI = Exact 90% confidence intervals

The percentage of subjects reporting each local and general solicited symptom, along with the incidence of grade 3 symptoms occurring within the 4-day follow-up after booster vaccination, is summarised in Table 4.

Document 1

Name of company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of finished product:** **Name of active substance:** DTPa-IPV/Hib	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Table 4: Percentage of subjects reporting each solicited local and general symptom, reported during the 4-day follow-up period after booster vaccination (ATP cohort for reactogenicity)

Symptoms		Group 1 N= 100* n	%	95% CI		Group 2 N=98 n	%	95% CI	
Pain at injection site	Any	56	56.0	45.7	65.9	60	61.2	50.8	70.9
	Grade 3	4	4.0	1.1	9.9	11	11.2	5.7	19.2
Redness at injection site	Any	58	58.0	47.7	67.8	65	66.3	56.1	75.6
	>20mm	26	26.0	17.7	35.7	24	24.5	16.4	34.2
Swelling at injection site	Any	39	39.0	29.4	49.3	49	50.0	39.7	60.3
	>20mm	19	19.0	11.8	28.1	18	18.4	11.3	27.5
Irritability	Any	44	44.0	34.1	54.3	45	45.9	35.8	56.3
	Grade 3	1	1.0	0.0	5.4	3	3.1	0.6	8.7
Loss of appetite	Any	25	25.0	16.9	34.7	26	26.5	18.1	36.4
	Grade 3	1	1.0	0.0	5.4	3	3.1	0.6	8.7
Restlessness	Any	35	35.0	25.7	45.2	41	41.8	31.9	52.2
	Grade 3	1	1.0	0.0	5.4	3	3.1	0.6	8.7
Sleeping more than usual	Any	24	24.0	16.0	33.6	27	27.6	19.0	37.5
	Grade 3	0	0.0	0.0	3.6	1	1.0	0.0	5.6
Fever (Rectal temperature)	≥ 38°C	29	29.0	20.4	38.9	38	38.8	29.1	49.2
	≥39.6°C	0	0.0	0.0	3.6	2	2.0	0.2	7.2

N = number of subjects with a symptom sheet completed
n / % = number / percentage of subjects reporting a specified symptom
95% CI= Exact 95% confidence intervals
Any = any local symptom reported regardless of intensity
Grade 3 pain = the child cried when the limb was moved /spontaneously painful (prevented normal activity).
Grade 3 irritability = crying that could not be comforted. For all other solicited symptoms, Grade 3 defined as an adverse experience which prevents normal everyday activities.
Not shown are the least frequently reported solicited symptoms: the incidence of diarrhea was less than 10% per group and the incidence of vomiting was 2% or less.
*One subject did not return his diary card.

- Most solicited symptoms were assessed as grade 1 or 2 in intensity and had an onset within the first two days after vaccination.
- Redness was the most frequently reported local symptom, irritability the most frequently reported general symptom.
- Extensive swelling (defined as swelling with a diameter >50 mm, noticeable diffuse swelling or noticeable increase of limb circumference) was reported in 7.9% of subjects in group 1 and in 7.1% in group 2. No swelling involving the adjacent joint or functional impairment was reported, and all reports of extensive swelling resolved without sequaelae (outcome for one event was unknown).

Name of company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of finished product:** **Name of active substance:** DTPa-IPV/Hib	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

- The percentage of subjects reporting unsolicited symptoms was similar between groups.
- Four subjects reported a serious adverse event (SAE), one in group 1 and three in group 2. All SAEs reported were assessed by the investigator as not related to vaccination. All subjects recovered without sequelae (except for one event in which the outcome was unknown).
- There were no dropouts due to an SAE.

Conclusions:

- Post-booster anti-PRP antibody titres were equivalent after booster vaccination with either Hib-TH or Hib-TB when mixed extemporaneously with DTPa-IPV; the 90% CI of the GMT ratio (1.171;1.966) was within the clinical limit defining equivalence [0.5;2].
- Antibody persistence approximately 11 months after completion of a 3-dose primary vaccination course of DTPa-IPV/Hib was similar between groups receiving Hib-TH or Hib-TB. Anti-PRP antibody persistence remained high in both groups (94.8% and 93.5% of the subjects in DTPa-IPV/Hib-TH and DTPa-IPV/Hib-TB groups still had anti-PRP titres ≥ 0.15µg/ml).
- The data demonstrate the equivalence of the two Hiib vaccine formulations Hib-TH and Hib-TB, mixed with DTPa-IPV in terms of immunogenicity of all antigens except FHA, when given as a booster dose in the second year of life. For the FHA vaccine response, although the absolute difference between the 2 groups did not exceed 10% (94.6% and 97.9% in DTPa-IPV/Hib-TH and DTPa-IPV/HIB-TB groups respectively), the greatest 90% CI limit on treatment difference (11.6%) marginally exceeded the *a priori* 10% clinical limit for equivalence.
- No substantial difference with regard to reactogenicity was observed between the Hib-TH and Hib-TB vaccines when mixed with GSK Biologicals' DTPa-IPV and given as a booster dose.

Date of report: 28 January 2002

Document 1

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** Combined DTPa-IPV vaccine (Infanrix™-IPV) **Name of active substance:** Diphtheria and tetanus toxoids, acellular pertussis and inactivated poliovirus	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Title of the study: Open, randomized, phase IIIb, multi-site, clinical study to compare the immunogenicity and reactogenicity of GSK Biologicals' DTPa-IPV vaccine, with GSK Biologicals' DTPa (Infanrix™) and Aventis MSD's IPV vaccine (Imovax Polio®) administered separately to healthy children 4 to 6 years of age, previously vaccinated with three doses of DTPa and IPV or OPV vaccines during the first year of life in a 3, 5 and 11 to 12 month schedule.

Principal Investigators: s22 and s22

Study sites: The study was performed at multiple sites in Italy and Sweden.

Publication (reference): Not published as of 18 December 2002.

Study period:	Date of first visit: January 17, 2002 Date of last visit: July 11, 2002	**Clinical phase:** IIIb

Objectives:

Primary:

- To demonstrate that the DTPa-IPV vaccine is at least equivalent to DTPa + IPV vaccines administered separately, in terms of immunogenicity to all vaccine antigens one month after vaccination at 4-6 years of age.

Non inferiority was reached if, one month after vaccination,

- *the upper limit of the two-sided 95% CI for the absolute group difference (DTPa + IPV vaccine group minus DTPa-IPV vaccine group) in seroprotection rate was below 10% for each of D, T and polio antigens,*

AND

- *the upper limit of the two-sided 95% CI for the group GMC ratio (DTPa + IPV vaccine group over DTPa-IPV vaccine group) was below 1.5 for each of PT, FHA and PRN pertussis antigens.*

Secondary:

- To assess the safety and reactogenicity of the study vaccines administered in both groups.

Methodology:

Study design: Open, randomized, multi-site study with two parallel groups with balanced allocation (1:1)
Group DTPa-IPV: Subjects received a single injection of the DTPa-IPV (Infanrix™-IPV) vaccine.
Group DTPa + IPV: Subjects received separate injections of DTPa (Infanrix™) and IPV (Imovax-Polio®) vaccines.

Number of subjects:

Planned: 424 eligible subjects (212 in each group) to obtain 380 evaluable subjects (190 in each group)
Enrolled: 417 subjects (212 in Group DTPa-IPV and 205 in Group DTPa + IPV)
Completed: 413 (no drop-outs due adverse events (AEs) or serious adverse events (SAEs))
Analysed for immunogenicity:
According to Protocol (ATP) immunogenicity cohort: 403 subjects (208 in Group DTPa-IPV and 195 in Group DTPa + IPV)
Analysed for safety:
Total cohort: 416 subjects (211 in Group DTPa-IPV and 205 in Group DTPa + IPV)

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** Combined DTPa-IPV vaccine (Infanrix™-IPV) **Name of active substance:** Diphtheria and tetanus toxoids, acellular pertussis and inactivated poliovirus	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Diagnosis and criteria for inclusion: Healthy children between and including 4 to 6 years of age at the time of vaccination, free of obvious health problems as established by medical history and clinical examination before entering into the study, with written informed consent obtained from parents or guardians of the subject. Subjects were previously vaccinated with three doses of DTPa and IPV/OPV vaccines at 3, 5 and 11 to 12 months of age. An additional dose of OPV was given to Italian subjects at 3 years of age.

Test product, dose, mode of administration, lot numbers:

- GSK Biologicals' combined DTPa-IPV vaccine (Infanrix™-IPV) containing per 0.5 ml dose: Diphtheria toxoid ≥ 30 IU or 25 Lf; Tetanus toxoid ≥ 40 IU or 10 Lf; Pertussis toxoid (PT) 25 µg; Filamentous haemagglutinin (FHA) 25 µg; Pertactin (PRN) 8 µg; Poliovirus type 1: 40 D Ag units; type 2: 8 D Ag units; type 3: 32 D Ag units; Aluminium as salts 0.5 mg; 2-phenoxyethanol ≤2.5 mg; Sodium chloride 150 mM; Formalin ≤100 mcg; Neomycin sulpbate ≤25 mcg; Polysorbate ≤50 mcg. Lot no. 20779C9 was used.

Mode of administration: Administered as a single intramuscular injection in the deltoid.

Reference therapy, dose and mode of administration, lot number:

- GSK Biologicals' DTPa vaccine (Infanrix™) containing per 0.5 ml dose: Diphtheria toxoid ≥ 30 IU or 25 Lf; Tetanus toxoid ≥ 40 IU or 10 Lf; PT 25 µg; FHA 25 µg; PRN 8 µg; Aluminium as salts 0.5 mg; 2-phenoxyethanol ≤2.5 mg; Sodium chloride 150 mM. Lot no. 14959A9 was used.
- Aventis MSD's IPV vaccine (Imovax Polio®) containing per 0.5 ml dose: Poliovirus type 1: 40 D Ag units; type 2: 8 D Ag units; type 3: 32 D Ag units. Commercial lots were used.

Mode of administration: Administered as separate intramuscular injections in the deltoid.

Duration of treatment: Duration of study was one month for each subject.

Criteria for evaluation:

Immunogenicity: Measurement of serum concentration/titres of antibodies against all vaccine antigens at the time of the booster dose and at one month after the booster dose in all subjects.

Primary endpoints:

- Seroprotection one month after vaccination defined as:
  - percentage of subjects with anti-diphtheria antibody concentrations ≥ 0.1 IU/ml by ELISA
  - percentage of subjects with anti-tetanus antibody concentrations ≥ 0.1 IU/ml
  - percentage of subjects with anti-polio type 1 antibody titre ≥ 8
  - percentage of subjects with anti-polio type 2 antibody titre ≥ 8
  - percentage of subjects with anti-polio type 3 antibody titre ≥ 8
- Anti-PT, anti-FHA and anti-PRN antibody concentrations one month after vaccination.

Secondary endpoints:

- Anti-diphtheria, anti-tetanus, and anti-polio type 1, 2 and 3 antibody concentrations/titres one month after vaccination.
- Percentage of subjects with a vaccine response to PT, FHA and PRN one month after vaccination, defined as appearance of antibodies in subjects who are initially (i.e. before vaccination) seronegative or at least a two-fold increase in antibody concentrations between pre- and post- vaccination in subjects who are initially seropositive.
- Percentage of subjects with diphtheria neutralizing antibodies ≥ 0.016 IU/ml by Vero cell testing one month after vaccination.
- Seropositivity status one month after vaccination, defined as:
  - percentage of subjects with anti-PT, anti-FHA and anti-PRN antibody concentrations ≥ 5 EL.U/ml.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium Name of Finished Product: Combined DTPa-IPV vaccine (Infanrix™-IPV) Name of active substance: Diphtheria and tetanus toxoids, acellular pertussis and inactivated poliovirus	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** Volume: Page:	(for national authority only)

Safety: Recording of solicited local (pain, redness and swelling at each injection site) and general (fever, irritability/fussiness, loss of appetite and drowsiness) adverse events by the parents/guardians during the 4-day (Day 0-Day 3) follow-up period after vaccination. Recording of unsolicited adverse events occurring during the 31-day (Day 0-Day 30) follow-up period after vaccination and reporting of SAEs occurring throughout the study period. Parents/guardians were also instructed to contact the investigator immediately should their child manifest any symptoms that raised concern, including injection site swelling > 50 mm in diameter, diffuse swelling or a noticeable increase in limb circumference of the injected limb.

The safety endpoints (secondary endpoints) were:

- Occurrence of each solicited local symptom within the 4-day (Day 0-3) solicited follow-up period after vaccination.
- Occurrence of each solicited general symptom within the 4-day (Day 0-3) solicited follow-up period after vaccination.
- Occurrence of unsolicited symptoms within the 31-day (Day 0-30) follow-up period after vaccination.
- Occurrence SAEs throughout the entire study, up to and including 30 days post-vaccination.

Statistical methods: The analyses were performed using the Statistical Analysis Systems (SAS) 8.02 on Windows NT 4.0 and StatXact 5.0 procedure on SAS:

Demographics: Tabulation of demographic characteristics (age in years, race and gender) with calculation of mean age (plus range and standard deviation) for subjects included in the ATP and total cohorts.

Immunogenicity: Descriptive analysis: Immunogenicity analysis was performed only on the ATP cohort (primary analysis) since the percentage of subjects excluded from the ATP immunogenicity cohort did not exceed 5%. Calculation of seropositivity, seroprotection or vaccine response rates and Geometric Mean Concentrations/Titres (GMCs/Ts) with 95% Confidence Intervals (95% CI) for antibodies to each vaccine antigen and at each blood sampling time point.

Inferential analyses: Calculation of the asymptotic 95% CI for difference in seroprotection rates for anti-diphtheria, anti-tetanus and anti-polio type 1, 2 and 3 antibodies one month after vaccination between groups (DTPa + IPV *minus* DTPa-IPV). Calculation of the 95% CI for difference in the proportions of subjects showing a vaccine response to PT, FHA and PRN one month after vaccination between groups (DTPa + IPV *minus* DTPa-IPV). Calculation of the 95% CIs for the ratio of GMC/T for each vaccine antigen between groups (DTPa+ IPV over DTPa-IPV).

The primary objective was reached if:

- the upper limits of the asymptotic 95% CIs for differences in the seroprotection rates for anti-diphtheria, anti-tetanus and anti-polio type 1, 2 and 3 antibodies one month after vaccination between groups were less than 10%, and
- the upper limits of the 95% CIs for the ratio of GMC for anti-PT, anti-FHA and anti-PRN between groups were less than 1.5.

Reactogenicity: Reactogenicity analysis was performed only on the total cohort (primary analysis) since less than 5% of subjects were excluded from the ATP safety cohort. The percentage of subjects reporting any solicited symptoms during the 4-day follow-up period and any unsolicited symptoms during the 31-day follow-up period were computed with 95% CI by group according to the type of symptoms, their intensity and relationship to vaccination. The percentage of subjects having received anti-pyretic medication within the 31 days post-vaccination was evaluated. SAEs were described.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** Combined DTPa-IPV vaccine (Infanrix™-IPV) **Name of active substance:** Diphtheria and tetanus toxoids, acellular pertussis and inactivated poliovirus	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER **Volume:** **Page:**	(for national authority only)

RESULTS: The mean age of the ATP immunogenicity cohort at the time of booster dose was 5 years (range 4-6 years). The two groups were comparable in terms of demographic characteristics.

Immunogenicity results:

Before the booster dose, the percentages of subjects with antibody levels above the assay cut-off were similar between the groups. Tables 1 and 2 present the differences between groups for each immunogenicity endpoint. One month after booster vaccination, virtually all subjects in each group had seroprotective levels of anti-diphtheria, anti-tetanus and anti-polio types 1, 2 and 3 antibodies. Moreover, the majority of subjects had anti-diphtheria (> 95%) and anti-tetanus (> 98%) antibody concentrations ≥ 1 IU/ml. The majority of subjects showed a vaccine response to each of the pertussis antigens. GMC/Ts increased substantially after the booster dose as compared to the pre-vaccination values.

Table 1: Differences in seroprotection/vaccine response rates one month after booster vaccination, with their asymptotic 95% CIs (ATP immunogenicity cohort)

	DTPa-IPV		DTPa + IPV		DTPa + IPV *minus* DTPa-IPV		
Endpoints	**N**	**%**	**N**	**%**	**Difference**	**95% CI**	
Anti-D (% ≥ 0.1 IU/ml)	208	99.0	195	100	0.96	-0.98	3.44*
Anti-T (% ≥ 0.1 IU/ml)	208	100	195	100	0.00	-1.93	1.81*
Anti-PT (% VR)	200	98.5	186	99.5	0.96	-1.61	3.84
Anti-FHA (% VR)	201	96.0	189	98.9	2.92	-0.27	6.73
Anti-PRN (% VR)	201	98.0	189	100	1.99	-0.02	5.00
Anti-polio 1 (% ≥ 8)	193	100	186	100	0.00	-2.02	1.95*
Anti-polio 2 (% ≥ 8)	197	100	183	100	0.00	-2.06	1.91*
Anti-polio 3 (% ≥ 8)	189	99.5	175	100	0.53	-1.62	2.94*

N = number of subjects with available results, %= percentage of subjects with concentration/titre within the specified range
Vaccine response definition: appearance of antibodies (i.e. concentration ≥ cut-off 5 EL.U/ml) in subjects who were initially seronegative or at least 2-fold increase in antibody concentrations in those who were initially seropositive.
*Upper limit of the 95%CI below the pre-specified clinical limit of non-inferiority (10%) for difference in seroprotection rates; 95% CIs for differences in vaccine response were exploratory evaluations

Table 2: Ratios of GMC/Ts one month after booster vaccination, with their 95% CIs (ATP immunogenicity cohort)

	DTPa-IPV		DTPa + IPV		DTPa + IPV over DTPa-IPV		
Antibody	**N**	**GMC/T**	**N**	**GMC/T**	**Ratio**	**95% CI**	
Anti-D(ELISA)	208	6.249	195	6.242	0.999	0.816	1.223
Anti-T	208	9.964	195	8.482	0.851	0.724	1.001
Anti-PT	208	63.2	192	77.9	1.23	1.03	1.47*
Anti-FHA	208	735.2	195	830.0	1.13	0.96	1.32*
Anti-PRN	208	995.6	195	1021.3	1.03	0.85	1.24*
Anti-Polio 1	193	2096.0	186	2763.9	1.319	1.088	1.598
Anti-Polio 2	197	1702.4	183	2735.6	1.607	1.328	1.944
Anti-Polio 3	189	2542.6	175	3274.4	1.288	1.017	1.630

N = number of subjects with available results
Units for GMCs: IU/ml for anti-D and anti-T; EL.U/ml for anti-PT, anti-FHA and anti-PRN antibodies
*Upper limit of the 95%CI below the pre-specified clinical limit of non-inferiority (1.5) for GMC ratios; 95% CIs for differences in GMC/T ratio for other antibodies were exploratory evaluations

Document 1

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium Name of Finished Product: Combined DTPa-IPV vaccine (Infanrix™-IPV) Name of active substance: Diphtheria and tetanus toxoids, acellular pertussis and inactivated poliovirus	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

Results of the inferential analyses demonstrate the non-inferiority of the DTPa-IPV vaccine *versus* separate concomitant injections of DTPa and IPV vaccines in terms of seroprotection to diphtheria, tetanus and each polio serotype, and in terms of anti-PT, anti-FHA and anti-PRN antibody GMCs one month after the booster dose. Indeed, the upper limits of the 95% CIs for the difference in seroprotection rates and ratio of GMCs as defined above were below the pre-defined clinical limit for non-inferiority.

Safety Results: The incidence of solicited local injection site symptoms and solicited general symptoms during the 4-day follow-up period (Day 0-3) after vaccination is presented in Table 3.

- The incidences of the solicited local and general symptoms were similar between the groups. Clinically significant solicited local and general symptoms, i.e. those rated as grade "3" in intensity, also occurred at similar rates in the two groups.

Table 3: Incidence of solicited local and general symptoms reported during the 4-day follow-up period (total cohort)

		DTPa-IPV				DTPa + IPV			
		n	%	95%CI LL	95%CI UL	n	%	95%CI LL	95%CI UL
Solicited local symptoms				N = 210				N = 201	
Pain	Any	150	71.4	64.8	77.4	139	69.2	62.3	75.5
	Grade 3¶	6	2.9	1.1	6.1	10	5.0	2.4	9.0
Redness	Any	128	61.0	54.0	67.6	124	61.7	54.6	68.4
	>50mm	54	25.7	19.9	32.2	64	31.8	25.5	38.8
Swelling	Any	112	53.3	46.3	60.2	109	54.2	47.1	61.3
	>50mm	28	13.3	9.0	18.7	33	16.4	11.6	22.3
Solicited general symptoms				N = 210				N = 202	
Fever*	≥ 38°C	44	21.0	15.7	27.1	34	16.8	11.9	22.7
	>39.5°C	1	0.5	0.0	2.6	3	1.5	0.3	4.3
Irritability	Total	35	16.7	11.9	22.4	40	19.8	14.5	26.0
	Grade 3§	0	0.0	0.0	1.7	2	1.0	0.1	3.5
Loss of appetite	Total	40	19.0	14.0	25.0	34	16.8	11.9	22.7
	Grade 3§	1	0.5	0.0	2.6	4	2.0	0.5	5.0
Drowsiness	Total	52	24.8	19.1	31.2	50	24.8	19.0	31.3
	Grade 3§	1	0.5	0.0	2.6	5	2.5	0.8	5.7

N = number of subjects with at least one symptom sheet completed
n/% = number/percentage of subjects reporting a specified symptom
*Measured rectally; ¶cried when limb was moved/spontaneously painful; § prevented everyday normal activities

- The incidences of the unsolicited symptoms including those rated as grade "3" in intensity or assessed as related to vaccination were similar between the groups.
- The percentages of subjects who received any medication or any antipyretic medication were similar between the two groups.
- Two subjects in the DTPa + IPV group reported a SAE, neither of which was assessed as related to vaccination by the investigator.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** Combined DTPa-IPV vaccine (Infanrix™-IPV) **Name of active substance:** Diphtheria and tetanus toxoids, acellular pertussis and inactivated poliovirus	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

- The parents/guardians of 11 subjects (4 in the DTPa-IPV group and 7 in the DTPa + IPV group) contacted the investigator during the study to report large injection site swelling reactions. Assessment of the extent and severity of the reaction was performed by the investigator (Table 4). Two of the subjects from the DTPa-IPV group had diffuse swelling, but adjacent joints were not involved and none had functional impairment. Two subjects from the DTPa + IPV group had diffuse swelling. For one of these subjects the swelling involved the adjacent joint, but functional impairment was mild. In this group, one subject had severe functional impairment (prevented normal everyday activities).
- In addition to these large injection site swelling reactions reports during the study, detailed information was sought at the end of the study for all subjects with local swelling > 50 mm. The parents of 52 additional subjects were thus questioned *post hoc*. The total information from the 63 subjects is shown in Table 4.
- The swellings typically occurred on Day 1 or Day 2 after vaccination and lasted less than 5 days for most cases. There was no functional impairment associated with the reaction in most of the swellings, and only mild impairment in another quarter of the cases. The average increase in arm circumference was of 2.2 cm. All swellings resolved spontaneously without sequelae.

Table 4: Large injection site swelling (total cohort)

	DTPa-IPV N = 210 n (%)		**DTPa + IPV N = 201 n (%)**	
Large injection site swelling	parental reports	all reports	parental reports	all reports
Local > 50 mm	2 (1.0)	21 (10.0)	5 (2.5)	27 (13.4)
Diffuse not involving adjacent joint	2 (1.0)	7 (3.3)	1 (0.5)	5 (2.5)
Diffuse involving adjacent joint	0	0	1 (0.5)	3 (1.5)

N = Number of subjects
n = Number of subjects with a report of the symptom
% = Percentage of subjects with a report of the symptom

CONCLUSIONS:

- GSK Biologicals' DTPa-IPV vaccine was immunogenic as a booster dose in healthy children 4 to 6 years of age, previously vaccinated with three doses of DTPa and IPV or OPV vaccines during the first year of life in a 3, 5 and 11 to 12 month schedule.
- GSK Biologicals' DTPa-IPV vaccine was non-inferior to separate concomitant injections of GSK Biologicals' DTPa (Infanrix™) and Aventis MSD's IPV vaccine (Imovax Polio®) in terms of immunogenicity to each component antigen.
- The incidence of large swelling reactions was similar in the two groups and within the range published for other DTPa vaccines given as a pre-school booster.
- The reactogenicity profile of a booster dose of GSK Biologicals' DTPa-IPV vaccine was similar to separate concomitant injections of GSK Biologicals' DTPa (Infanrix™) and Aventis MSD's IPV vaccine (Imovax Polio®).

Date of report: 18 December 2002

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** INFANRIX®-IPV, PRIORIX™ **Name of active substance:** Diphtheria and tetanus toxoids, pertussis antigens (PT, FHA and PRN), poliovirus types 1, 2 and 3, Schwarz measles strain, RIT 4385 mumps strain, RA 27/3 rubella strain.	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Title of the study: 213503/ 046 (DTaP-IPV-046)

Open, randomised phase IIIb, clinical trial to compare the immunogenicity and reactogenicity of GSK Biologicals' DTaP-IPV vaccine (INFANRIX®-IPV), with GSK Biologicals' DTaP (INFANRIX®) and Aventis Pasteur MSD's IPV vaccine (IPOL®) administered separately to healthy children 4 to 6 years of age, previously vaccinated with 4 doses of DTaP and polio vaccine, and co-administered with GSK Biologicals' MMR vaccine (PRIORIX™).

Principal Investigators: Center 1: s22 [redacted] Center 2: s22 [redacted]
Center 3: s22 [redacted] *(Amended 7 October 2004)*

Study Centers:

Center 1: Murdoch Children's Research Institute, Level 2/ 723 Swanston Street, Carlton 3010, Australia

Center 2: University of Adelaide, Women's and Children's Hospital, 72, King William road, North Adelaide 5006 Australia

Center 3: TVW Telethon for Child Health Research, Princess Margaret Hospital, Subiaco, WA, 6872, Australia

Publication (reference): Not published as of 5 March 2004

Study period: Date of first visit: 27 May 2002
Date of last visit: 15 January 2003

Clinical phase: IIIb

Objectives:

Primary:

- To demonstrate that the immunogenicity of the DTaP-IPV vaccine one month after vaccination is at least as good as that of DTaP and IPV administered separately, when both groups received a separate concomitant injection of the MMR vaccine.

  Criteria for meeting this objective (one month after vaccination):

  Upper limit of two-sided 95% CI for the absolute group difference in seroprotection rates below 10% for each of D, T and Polio antigens and

  Upper limit of two-sided 95% CI for the group GMT ratio below 1.5 for each of PT, FHA and PRN pertussis antigens.

Secondary:

- To assess the safety and reactogenicity of the study vaccines administered in both groups.
- To assess the immunogenicity of MMR vaccine antigens one month after vaccination.

Methodology:

Study design: Open, randomised (1:1), multicentric (3 centers) study with two parallel groups.
Group DTaP-IPV + MMR received GlaxoSmithKline (GSK) Biologicals' DTaP-IPV + GSK Biologicals' MMR at Visit 1 (Day 0).
Group DTaP + IPV + MMR received GSK Biologicals' DTaP + Aventis Pasteur MSD's IPV + GSK Biologicals' MMR at Visit 1 (Day 0).
Blood samples were drawn from all subjects on the day of vaccination (Day 0) and at one month after vaccination (Month 1).

Number of subjects:

Planned: 424 (212 per group); Vaccinated*: 362 (181 per group); Completed: 360 (180 per group)
Analysed for ATP safety: 338 (Group DTaP-IPV + MMR = 171; Group DTaP + IPV + MMR = 167)
Analysed for ATP immunogenicity: 329 (Group DTaP-IPV + MMR = 166; Group DTaP + IPV + MMR = 163). No subjects dropped out due to AEs.
*The eligibility criteria required that the subjects should have previously received 4 doses of DTaP based vaccines and should be within the age group of 4 to 6 years. As DTaP vaccines were only introduced into Australia for primary vaccination in 1999, this criterion was difficult to meet and it was decided to end the

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium Name of Finished Product: INFANRIX®-IPV, PRIORIX™ Name of active substance: Diphtheria and tetanus toxoids, pertussis antigens (PT, FHA and PRN), poliovirus types 1, 2 and 3, Schwarz measles strain, RIT 4385 mumps strain, RA 27/3 rubella strain.	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

trial with the available cohort of 366 enrolled subjects. The power of the study to meet the primary objective was still considered adequate (> 80%) with 366 subjects enrolled. Four subjects were eliminated as the study vaccine was not administered to them although they were allocated a subject number.

Diagnosis and criteria for inclusion: Healthy male or female infants aged between 4 and 6 years at the time of vaccination, free of obvious health problems as established by medical history and clinical examination before entry into the study. The subjects had completed primary vaccination with DTaP and polio vaccine at 2, 4 and 6 months and received a DTaP booster and vaccination against MMR (mumps, measles and rubella) in the second year of life. Written informed consent was received from the parent/guardian prior to study entry.

Test product, dose, mode of administration, lot No.:
Vaccination schedule/site: A single dose of DTaP-IPV vaccine (INFANRIX®-IPV) was administered as a deep intramuscular (IM) injection in the left deltoid region. GSK Biologicals' MMR (PRIORIX™) vaccine was administered subcutaneously in the upper right deltoid region.
Vaccine/composition/dose/lot number: Each 0.5 ml of GSK Biologicals' INFANRIX®-IPV vaccine contained ≥ 30 International Units (25 Limit flocculation) of diphtheria toxoid, ≥ 40 IU (10 Lf) of tetanus toxoid, 25 µg of pertussis toxoid (PT), 25 µg of filamentous hemagglutinin (FHA), 8 µg of pertactin (PRN), 40D Ag units of poliovirus type 1, 8D Ag units of poliovirus type 2, 32D Ag units of poliovirus type 3, 0.5 mg of aluminium salts and ≤ 2.5 mg of 2-phenoxyethanol. Lot No.:20787A9
Each 0.5 ml of GSK Biologicals' PRIORIX™ vaccine contained: ≥ 103.0 TCID50 of Schwarz measles strain, ≥ 103.7 TCID50 of RIT 4385 mumps strain and ≥ 103.0 TCID50 of RA 27/3 rubella strain. Lot No.: MJR422A44

Reference therapy, dose and mode of administration, lot No.:
Vaccination schedule/site: A single dose of GSK Biologicals' DTaP vaccine (INFANRIX®) vaccine was administered as a deep IM injection in the left deltoid. GSK Biologicals' MMR (PRIORIX™) and Aventis Pasteur MSD's IPV vaccine (IPOL®) were administered subcutaneously in the upper right deltoid region and lower right deltoid region, respectively.
Vaccine/composition/dose/lot number: Each 0.5 ml of GSK Biologicals' INFANRIX® vaccine contained: ≥ 30 IU (25 Lf) of diphtheria toxoid, ≥ 40 IU (10 Lf) of tetanus toxoid, 25 µg of PT, 25 µg of FHA, 8 µg of PRN, 0.5 mg of aluminium as salt and ≤ 2.5 mg of 2-phenoxyethanol. Lot No.: 14959A9
Each 0.5 ml of Aventis Pasteur MSD's IPV vaccine (IPOL®) contained: 40D Ag units of poliovirus type 1, 8D Ag units of poliovirus type 2 and 32D Ag units of poliovirus type 3. Lot No.: T1291-2
The composition and lot no. of GSK Biologicals' PRIORIX™ vaccine was the same as in the test group.

Duration of treatment: The duration of the study was approximately one month per subject.

Criteria for evaluation:
Primary endpoints: Immunogenicity:

- Seroprotection status for anti-poliovirus type 1, 2 and 3 antibodies (antibody titer ! 8), anti-diphtheria antibodies (antibody concentration ! 0.1 IU/ml by ELISA, or diphtheria neutralising antibodies ! 0.016 IU/ml by VERO cell testing in subjects seronegative by ELISA testing one month after vaccination) and anti-tetanus antibodies (antibody concentration ! 0.1 IU/ml).
- Anti-PT, anti-PRN and anti-FHA antibody concentrations.

Secondary endpoints: Immunogenicity

- Seropositivity status for anti-PT, anti-FHA and anti-PRN antibodies (≥ 5 EL.U/ml), anti-mumps antibodies (≥ 231 U/ml), anti-measles antibodies (≥ 150 mIU/ml), anti-rubella antibodies (≥ 4 IU/ml and ≥ 10 IU/ml).
- Anti-poliovirus type 1, anti-poliovirus type 2 and anti-poliovirus type 3 antibody titers
- Anti-diphtheria toxoid, anti-tetanus toxoid, anti-measles, anti-mumps and anti-rubella antibody concentrations.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium Name of Finished Product: INFANRIX®-IPV, PRIORIX™ Name of active substance: Diphtheria and tetanus toxoids, pertussis antigens (PT, FHA and PRN), poliovirus types 1, 2 and 3, Schwarz measles strain, RIT 4385 mumps strain, RA 27/3 rubella strain.	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

- Vaccine response to PT, PRN and FHA defined as appearance of antibodies in subjects who were initially (i.e. at pre-vaccination) seronegative or at least experienced a two-fold increase in antibody concentrations between pre and post-vaccination in subjects who were initially seropositive.

Safety and reactogenicity

- Occurrence of solicited local (pain, redness and swelling) and general (fever, irritability /fussiness, drowsiness and loss of appetite) symptoms during the 4-day follow-up period after vaccination.
- Occurrence of specific solicited general symptoms (fever, rash/exanthema, parotid/salivary gland swelling and any suspected signs of meningism including febrile convulsions) during the 15-day follow-up period after MMR vaccination.
- Occurrence of unsolicited symptoms during the 31-day follow-up period after vaccination.
- Occurrence of serious adverse events throughout the study period.

Statistical methods: Analysis was carried out on the vaccinated cohort and two ATP cohorts. The primary cohort for immunogenicity was the ATP immunogenicity cohort. As opposed to the protocol, the ATP safety cohort was primarily used for safety as it excluded the subjects with DTPw vaccine history that were erroneously enrolled in the study.

Analysis of demographics: Demographic characteristics (age in years, gender, race and vaccination history) were tabulated per group. The distribution of the subjects enrolled among study centers was also tabulated per group.

Analysis of immunogenicity:

Descriptive analysis: Seropositivity/ seroprotection rates to each vaccine antigen and their 95% confidence interval (CI) were tabulated for both groups. The Geometric mean concentration/ titers (GMC/GMTs) and their 95%CI were also calculated. The percentage of subjects with vaccine response to PT, FHA and PRN with their exact 95% CI, one month after vaccination was calculated for each group. Distribution of anti-diphtheria, anti-tetanus, anti-PT, anti-PRN, anti-FHA, anti-measles, anti-mumps and anti-rubella antibody concentrations and anti-poliovirus types 1, 2 and 3 antibody titers were displayed using reverse cumulative curves (RCCs), one month after vaccination.

Inferential analysis: The standardized asymptotic two-sided 95% CI for the group difference in seroprotection rates for anti-diphtheria, anti-tetanus and anti-poliovirus types 1, 2 and 3 antibodies, one month after vaccination, were calculated. The two-sided 95% CI for the ratio of GMCs for the pertussis antigens (anti-PT, anti-PRN and anti-FHA) between the two groups were computed using a one-way ANCOVA model on the logarithm10 transformation of the titers. The model included groups as fixed effect and pre-vaccination measurement as co-variable.

Exploratory analysis: The standardized asymptotic two-sided 95% CI for the group difference in the percentage of subjects showing vaccine response to PT, FHA and PRN, one month after vaccination were calculated. The two-sided 95% CI for the ratio of GMC/ GMTs for anti-diphtheria, anti-tetanus and anti-poliovirus types 1, 2 and 3 antibodies, anti-measles, anti-mumps and anti-rubella antibodies were computed using a one-way ANCOVA model on the logarithm10 transformation of the antibody concentrations/titers. The model included groups as fixed effect and pre-vaccination measurement as co-variable.

Analysis of safety: All safety analyses were descriptive.

Percentage (with exact 95% CI) of subjects reporting at least one local adverse event, at least one general adverse event (solicited or unsolicited) and any adverse event during the 4-day follow-up period after vaccination was calculated per group. The percentage (with exact 95% CI) of subjects reporting each solicited symptom was calculated by group over the solicited follow-up period.

The same calculations were done for each solicited local symptom rated as grade "2" or "3" in intensity, for each solicited symptom rated as grade "3" in intensity and for each solicited general symptoms assessed as related to vaccination. For each group, the percentage of subjects reporting each MMR

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** INFANRIX®-IPV, PRIORIX™ **Name of active substance:** Diphtheria and tetanus toxoids, pertussis antigens (PT, FHA and PRN), poliovirus types 1, 2 and 3, Schwarz measles strain, RIT 4385 mumps strain, RA 27/3 rubella strain.	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

specific solicited general symptom, with a reasonable possibility to be related to vaccination and with a grade "3" intensity over the 15-day follow-up period was tabulated along with exact 95% CIs.
Percentage of subjects reporting unsolicited symptoms and those with causal relationship to vaccination, classified by WHO Preferred Terms, during the 31-day follow-up period after vaccination were tabulated with its 95% CI. Percentage of subjects receiving concomitant medication (any medications, antipyretics, and prophylactic antipyretics) during the 4-day and 31-day follow-up period after vaccination was tabulated by group.

SUMMARY-CONCLUSIONS:

Demography: The mean age of the ATP immunogenicity cohort at the time of vaccination was four years with a standard deviation of 0.2 years. The female to male ratio was 1.26. The majority of subjects (97.6%) in both groups were white.

Immunogenicity: The primary analysis was done on the ATP immunogenicity cohort.
Prior to booster vaccination, seroprotection and seropositivity rates were similarly high in the two groups. One month after vaccination, all subjects in both groups had seroprotective antibody levels against diphtheria, tetanus, poliovirus types 1, 2 and 3 antigens and majority of subjects showed vaccine response to all three pertussis antigens (PT, FHA and PRN). Despite the initial high seroprotection and seropositivity rates, marked increases in post-vaccination GMC/GMTs were observed.
The upper limit of the asymptotic two-sided 95% CI for the difference in seroprotection rates and ratio of GMCs as defined above were below the pre-defined clinical limit for non-inferiority. Therefore, it can be concluded that the DTaP-IPV vaccine is non-inferior to DTaP and IPV vaccines administered separately in terms of seroprotection to diphtheria, tetanus, each of the polio serotypes and in terms of anti-PT, anti-FHA and anti-PRN antibody concentrations *(Amended 7 October 2004)*.
The exploratory analysis on GMC ratios is also consistent with the similarity of the reponse in the two groups.

Table 1. Differences in seroprotection/vaccine response (for pertussis antigens) rates one month after booster vaccination, with their asymptotic 95% CIs (ATP immunogenicity cohort)

Endpoints	Group DTaP-IPV + MMR		Group DTaP + IPV + MMR		DTaP + IPV + MMR minus DTaP-IPV+ MMR		
	N	%	N	%	Difference	95%CI	
						LL	UL
Anti-diphtheria ≥ 0.1 IU/ml	165	100.0	159	100.0	0.0	– 2.4	2.3*
Anti-tetanus ≥ 0.1 IU/ml	165	100.0	159	100.0	0.0	– 2.3	2.4*
Anti-PT (2 fold increase)	159	98.7	148	99.3	0.6	–1.8	3.1
Anti-FHA (2 fold increase)	159	96.9	148	99.3	2.5	–0.2	5.7
Anti-PRN (2 fold increase)	159	98.1	150	100.0	1.9	0.1	4.6
Anti-poliovirus type 1 ≥ 8	156	100.0	151	100.0	0.0	– 2.5	2.4*
Anti-poliovirus type 2 ≥ 8	153	100.0	152	100.0	0.0	– 2.5	2.4*
Anti-poliovirus type 3 ≥ 8	148	100.0	147	100.0	0.0	– 2.5	2.5*

N: number of subjects with available data
%: percentage of subjects with seroprotective antibody levels post-vaccination
Difference: Difference between the two groups in percentage of seroprotected subjects (Group DTaP + IPV + MMR minus Group DTaP-IPV + MMR)
95% CI: Standardised asymptotic two-sided 95% confidence interval; LL: Lower Limit; UL: Upper Limit
* Upper limit of 95% CI below the pre-specified clinical limit of non-inferiority (10%) for difference in seroprotection rates. 95% CI for the differences in vaccine response were exploratory evaluations

Doc ID 1

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium Name of Finished Product: INFANRIX®-IPV, PRIORIX™ Name of active substance: Diphtheria and tetanus toxoids, pertussis antigens (PT, FHA and PRN), poliovirus types 1, 2 and 3, Schwarz measles strain, RIT 4385 mumps strain, RA 27/3 rubella strain.	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

Table 2: Ratios of GMC/Ts one month after booster vaccination, with their 95% CIs (ATP immunogenicity cohort)

Antibody	Group DTaP-IPV + MMR		Group DTaP + IPV + MMR		DTaP + IPV + MMR over DTaP-IPV + MMR		
	N	GMC/T	N	GMC/T	Ratio	95%CI LL	95%CI UL
Anti-diphtheria	159	6.220	150	5.859	0.942	0.796	1.115
Anti-tetanus	159	8.222	150	6.644	0.808	0.714	0.914
Anti-PT	159	112.71	148	128.34	1.139	0.950	1.365*
Anti-FHA	159	360.29	148	429.72	1.193	1.030	1.382*
Anti-PRN	159	703.80	150	676.11	0.961	0.819	1.127*
Anti-poliovirus type 1	145	2985.66	142	3258.44	1.091	0.877	1.358
Anti-poliovirus type 2	142	3012.87	143	3514.47	1.166	0.950	1.433
Anti-poliovirus type 3	138	4898.58	137	4813.27	0.983	0.815	1.184
Anti-measles	163	2657.54	161	2579.88	0.971	0.865	1.090
Anti-mumps	153	2446.70	158	2243.26	0.917	0.808	1.040
Anti-rubella	163	140.57	162	155.81	1.108	1.009	1.217

N: number of subjects with pre- and post-vaccination results
Ratio: ratio between the two groups in terms of GMC/Ts (DTaP + IPV + MMR over DtaP-IPV + MMR)
GMC/T: Geometric Mean Concentrations/Titers adjusted for baseline concentration
95% CI: Two-sided 95% confidence interval; LL: Lower Limit; UL: Upper Limit
*Upper limit of 95% CI below the pre-specified clinical limit of non-inferiority (1.5) for GMC/T ratios. 95% CI for GMC/T ratios for other antigens were exploratory evaluations.

Table 3: Seropositivity rates and GMCs after MMR booster vaccination, one month after the booster dose (ATP immunogenicity cohort)

Antibodies	Group DTaP-IPV + MMR							Group DTaP + IPV + MMR						
	N	S+ (%)	95%CI LL	95%CI UL	GMC	95%CI LL	95%CI UL	N	S+ (%)	95%CI LL	95%CI UL	GMC	95%CI LL	95%CI UL
Anti-mumps	153	100.0	97.6	100.0	2437.7	2159.5	2751.6	158	100.0	97.7	100.0	2251.3	2037.6	2487.5
Anti-measles	163	100.0	97.8	100.0	2549.9	2236.6	2907.2	161	99.4	96.6	100.0	2690.1	2379.7	3041.0
Anti-rubella	163	100.0	97.8	100.0	139.7	128.5	151.9	162	100.0	97.7	100.0	156.8	146.2	168.1

N: number of subjects with available results
GMC: Geometric mean concentrations
S+: Antibody concentration ≥ assay cut-off (cut-off for mumps: 231 U/ml, measles: 150 mIU/ml, rubella: 4 IU/ml)
%: Percentage of seropositive subjects
95% CI: 95% confidence interval; LL: Lower Limit; UL: Upper Limit

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium Name of Finished Product: INFANRIX®-IPV, PRIORIX™ Name of active substance: Diphtheria and tetanus toxoids, pertussis antigens (PT, FHA and PRN), poliovirus types 1, 2 and 3, Schwarz measles strain, RIT 4385 mumps strain, RA 27/3 rubella strain.	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

The immune response to the concomitantly administered MMR vaccine was in line with previously reported responses to a second dose of this vaccine.
Safety: Primary analysis was done on the ATP safety cohort.
Table 4: Incidence of solicited local and general symptoms for the ATP safety cohort

		Group DTaP-IPV + MMR (N = 171)				Group DTaP + IPV + MMR (N = 167)			
		n	%	95%CI LL	95%CI UL	n	%	95%CI LL	95%CI UL
Solicited local symptoms (Day 0 to Day 3 post-vaccination)									
Pain	Any	139	81.3	74.6	86.8	126	75.4	68.2	81.8
	Grade "3"	12	7.0	3.7	11.9	8	4.8	2.1	9.2
Redness	Any	138	80.7	74.0	86.3	149	89.2	83.5	93.5
	> 50 mm	56	32.7	25.8	40.3	70	41.9	34.3	49.8
Swelling	Any	106	62.0	54.3	69.3	126	75.4	68.2	81.8
	> 50 mm	41	24.0	17.8	31.1	47	28.1	21.5	35.6
Solicited general symptoms (Day 0 to Day 3 post-vaccination)									
Drowsiness	Any	40	23.4	17.3	30.5	40	24.0	17.7	31.2
	Grade "3"	5	2.9	1.0	6.7	3	1.8	0.4	5.2
Fever (axillary temperature)	Any	39	22.8	16.7	29.8	45	26.9	20.4	34.3
	> 39.0 °C	3	1.8	0.4	5.0	1	0.6	0.0	3.3
Irritability	Any	45	26.3	19.9	33.6	55	32.9	25.9	40.6
	Grade "3"	2	1.2	0.1	4.2	0	0.0	0.0	2.2
Loss of appetite	Any	35	20.5	14.7	27.3	40	24.0	17.7	31.2
	Grade "3"	4	2.3	0.6	5.9	3	1.8	0.4	5.2

N: Number of subjects having received at least one dose
n (%): Number (percentage) of subjects reporting a general or local symptom
Any site: n: Number of subjects presenting at least one local symptom whatever the number of injections.
Grade "3" symptoms: Symptoms that prevented normal daily activities
There was no difference between groups in terms of the incidence and intensity of solicited local and general symptoms. Solicited general symptoms of grade "3" intensity were uncommon (< 3%).
During the 15-day follow-up period after vaccination, the incidence of fever was similar in the two groups, with temperature > 39.0 °C reported for 4.1% and 5.4% of study subjects in the two groups. A similar proportion of subjects (21.6% and 20.4%) received antipyretics during the course of the study.
With respect to solicited symptoms specific to MMR vaccination, rash causally related to MMR vaccination was reported for 11 subjects in total. No cases of meningism were reported.

Doc ID 1

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium Name of Finished Product: INFANRIX®-IPV, PRIORIX™ Name of active substance: Diphtheria and tetanus toxoids, pertussis antigens (PT, FHA and PRN), poliovirus types 1, 2 and 3, Schwarz measles strain, RIT 4385 mumps strain, RA 27/3 rubella strain.	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

Table 5: Large injection site swelling and extent of the reaction for the ATP safety cohort

	DTaP-IPV (N = 171)		DTaP (N = 167)	
	n	%	n	%
Any large injection site swelling	42	24.56	49	29.34
Local > 50mm	31	18.13	30	17.96
Diffuse not involving adjacent joint	1	0.58	9	5.39
Involving at least one adjacent joint	10	5.85	10	5.99
• *Extending above the shoulder*	*4*	*2.34*	*2*	*1.19*
• *Upper arm swelling*	*2*	*1.17*	*2*	*1.19*
• *Whole-limb swelling*	*0*	*0.0*	*0*	*0.0*

N: Number of subjects having received at least one dose
n (%): Number (percentage) of subjects with a report of the symptom
Extending above the shoulder: Swelling extending past the shoulder joint, limited to the shoulder area.
Upper arm swelling: Swelling from the shoulder to the elbow (including both joints)
Whole-limb swelling: Swelling from the shoulder to the hand
Note: Symptoms in italics are a sub-classification of large swelling reactions involving at least one adjacent joint

Large swelling reactions at the site of injection of the DTaP based vaccine were reported for a similar percentage of subjects in the two groups. The majority of these swelling reactions were locally limited. In each group, ten subjects reported a reaction that involved the adjacent joint, i.e. the shoulder. Given that the vaccines were injected in the deltoid, this is not unexpected. Indeed, half of these reactions were limited to the shoulder area, with no further extension. For the other half, six extended above the shoulder with no further extension towards the elbow and four involved both the shoulder and the elbow joints. Only 2 subjects (DTaP-IPV vaccinees) reported functional impairment that prevented normal everyday activities. Large swellings occurred within 2 days post-vaccination and lasted less than 5 days for the majority of cases.

Unsolicited symproms: During the 31-day follow-up period after vaccination, the incidence of grade "3" unsolicited symptoms was similar in both groups. In the DTaP + IPV + MMR group, a larger percentage of subjects reported unsolicited injection site reactions and rhinitis determined by the investigator to be causally related to vaccination.

Serious adverse events (SAE): One subject (n° 420 in Group DTaP + IPV + MMR) reported an SAE, which was considered by the investigator to be causally related to vaccination. Three days after the vaccination, the subject developed high fever (40 °C) and headache. The next day he became lethargic and suffered from severe headache and loss of appetite. He was hospitalized, diagnosed with significant fever without infective focus and discharged from hospital. He was reviewed for persistent fever five days later and a diagnosis of concurrent non-serious bronchitis was made. The subject was treated with antibiotics and had recovered one week later.

There were no dropouts due to SAEs.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** INFANRIX®-IPV, PRIORIX™ **Name of active substance:** Diphtheria and tetanus toxoids, pertussis antigens (PT, FHA and PRN), poliovirus types 1, 2 and 3, Schwarz measles strain, RIT 4385 mumps strain, RA 27/3 rubella strain.	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Conclusions:

- GSK Biologicals' DTaP-IPV vaccine was immunogenic as a booster dose in children 4 to 6 years of age, previously vaccinated with three doses of DTaP and IPV or OPV vaccine during the first year of life and a booster dose of DTaP vaccine in the second year of life.
- The non-inferiority of the combined DTaP-IPV vaccine compared to separately administered DTaP and IPV was demonstrated in terms of immune response to each component antigen.
- The response to the concomitantly administered MMR vaccine was similar in the two groups and similar to previously reported responses for a second dose of this vaccine.
- No differences in the incidence and intensity of solicited symptoms were observed following vaccination with either DTaP-IPV + MMR or separately administered DTaP, IPV and MMR. Local reactions were observed more frequently than general symptoms and grade "3" general symptoms were rare.
- A similar incidence of large swelling reactions was observed after DTaP-IPV or DTaP booster vaccination. Incidences were within the range published for a fifth dose of DTaP vaccine at pre-school age. Upper arm swelling i.e. large injection site swellings involving both the shoulder and elbow joints occurred in 1.2% of the subjects.

Date of report: 5 March 2004 (Final)
Date of amendment: 7 October 2004

Document 1

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium Name of Finished Product: INFANRIX®-IPV, PRIORIX™ Name of active substance: Diphtheria and tetanus toxoids, pertussis antigens (PT, FHA and PRN), poliovirus types 1, 2 and 3, Schwarz measles strain, RIT 4385 mumps strain, RA 27/3 rubella strain.	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** Volume: Page:	(for national authority only)

Title of the study: 213503/046 (DTaP-IPV-046)
Open, randomised phase IIIb, clinical trial to compare the immunogenicity and reactogenicity of GSK Biologicals' DTaP-IPV vaccine (INFANRIX®-IPV), with GSK Biologicals' DTaP (INFANRIX®) and Aventis Pasteur MSD's IPV vaccine (IPOL®) administered separately to healthy children 4 to 6 years of age, previously vaccinated with 4 doses of DTaP and polio vaccine, and co-administered with GSK Biologicals' MMR vaccine (PRIORIX™).

Principal Investigators: Center 1: s22 Center 2: s22
Center 3: s22 *(Amended 7 October 2004)*

Study Centers:
Center 1: Murdoch Children's Research Institute, Level 2/ 723 Swanston Street, Carlton 3010, Australia
Center 2: University of Adelaide, Women's and Children's Hospital, 72, King William road, North Adelaide 5006 Australia
Center 3: TVW Telethon for Child Health Research, Princess Margaret Hospital, Subiaco, WA, 6872, Australia

Publication (reference): Not published as of 5 March 2004

Study period: Date of first visit: 27 May 2002
Date of last visit: 15 January 2003

Clinical phase: IIIb

Objectives:
Primary:
- To demonstrate that the immunogenicity of the DTaP-IPV vaccine one month after vaccination is at least as good as that of DTaP and IPV administered separately, when both groups received a separate concomitant injection of the MMR vaccine.
  Criteria for meeting this objective (one month after vaccination):
  Upper limit of two-sided 95% CI for the absolute group difference in seroprotection rates below 10% for each of D, T and Polio antigens and
  Upper limit of two-sided 95% CI for the group GMT ratio below 1.5 for each of PT, FHA and PRN pertussis antigens.

Secondary:
- To assess the safety and reactogenicity of the study vaccines administered in both groups.
- To assess the immunogenicity of MMR vaccine antigens one month after vaccination.

Methodology:
Study design: Open, randomised (1:1), multicentric (3 centers) study with two parallel groups.
Group DTaP-IPV + MMR received GlaxoSmithKline (GSK) Biologicals' DTaP-IPV + GSK Biologicals' MMR at Visit 1 (Day 0).
Group DTaP + IPV + MMR received GSK Biologicals' DTaP + Aventis Pasteur MSD's IPV + GSK Biologicals' MMR at Visit 1 (Day 0).
Blood samples were drawn from all subjects on the day of vaccination (Day 0) and at one month after vaccination (Month 1).

Number of subjects:
Planned: 424 (212 per group); Vaccinated*: 362 (181 per group); Completed: 360 (180 per group)
Analysed for ATP safety: 338 (Group DTaP-IPV + MMR = 171; Group DTaP + IPV + MMR = 167)
Analysed for ATP immunogenicity: 329 (Group DTaP-IPV + MMR = 166; Group DTaP + IPV + MMR = 163). No subjects dropped out due to AEs.
*The eligibility criteria required that the subjects should have previously received 4 doses of DTaP based vaccines and should be within the age group of 4 to 6 years. As DTaP vaccines were only introduced into Australia for primary vaccination in 1999, this criterion was difficult to meet and it was decided to end the

Doc ID REGU_200504_1491

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** INFANRIX®-IPV, PRIORIX™ **Name of active substance:** Diphtheria and tetanus toxoids, pertussis antigens (PT, FHA and PRN), poliovirus types 1, 2 and 3, Schwarz measles strain, RIT 4385 mumps strain, RA 27/3 rubella strain.	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** Volume: Page:	(for national authority only)

trial with the available cohort of 366 enrolled subjects. The power of the study to meet the primary objective was still considered adequate (> 80%) with 366 subjects enrolled. Four subjects were eliminated as the study vaccine was not administered to them although they were allocated a subject number.

Diagnosis and criteria for inclusion: Healthy male or female infants aged between 4 and 6 years at the time of vaccination, free of obvious health problems as established by medical history and clinical examination before entry into the study. The subjects had completed primary vaccination with DTaP and polio vaccine at 2, 4 and 6 months and received a DTaP booster and vaccination against MMR (mumps, measles and rubella) in the second year of life. Written informed consent was received from the parent/guardian prior to study entry.

Test product, dose, mode of administration, lot No.:
Vaccination schedule/site: A single dose of DTaP-IPV vaccine (INFANRIX®-IPV) was administered as a deep intramuscular (IM) injection in the left deltoid region. GSK Biologicals' MMR (PRIORIX™) vaccine was administered subcutaneously in the upper right deltoid region.
Vaccine/composition/dose/lot number: Each 0.5 ml of GSK Biologicals' INFANRIX®-IPV vaccine contained ≥ 30 International Units (25 Limit flocculation) of diphtheria toxoid, ≥ 40 IU (10 Lf) of tetanus toxoid, 25 µg of pertussis toxoid (PT), 25 µg of filamentous hemagglutinin (FHA), 8 µg of pertactin (PRN), 40D Ag units of poliovirus type 1, 8D Ag units of poliovirus type 2, 32D Ag units of poliovirus type 3, 0.5 mg of aluminium salts and ≤ 2.5 mg of 2-phenoxyethanol. Lot No.:20787A9
Each 0.5 ml of GSK Biologicals' PRIORIX™ vaccine contained: ≥ 103.0 TCID50 of Schwarz measles strain, ≥ 103.7 TCID50 of RIT 4385 mumps strain and ≥ 103.0 TCID50 of RA 27/3 rubella strain. Lot No.: MJR422A44

Reference therapy, dose and mode of administration, lot No.:
Vaccination schedule/site: A single dose of GSK Biologicals' DTaP vaccine (INFANRIX®) vaccine was administered as a deep IM injection in the left deltoid. GSK Biologicals' MMR (PRIORIX™) and Aventis Pasteur MSD's IPV vaccine (IPOL®) were administered subcutaneously in the upper right deltoid region and lower right deltoid region, respectively.
Vaccine/composition/dose/lot number: Each 0.5 ml of GSK Biologicals' INFANRIX® vaccine contained: ≥ 30 IU (25 Lf) of diphtheria toxoid, ≥ 40 IU (10 Lf) of tetanus toxoid, 25 µg of PT, 25 µg of FHA, 8 µg of PRN, 0.5 mg of aluminium as salt and ≤ 2.5 mg of 2-phenoxyethanol. Lot No.: 14959A9
Each 0.5 ml of Aventis Pasteur MSD's IPV vaccine (IPOL®) contained: 40D Ag units of poliovirus type 1, 8D Ag units of poliovirus type 2 and 32D Ag units of poliovirus type 3. Lot No.: T1291-2
The composition and lot no. of GSK Biologicals' PRIORIX™ vaccine was the same as in the test group.

Duration of treatment: The duration of the study was approximately one month per subject.

Criteria for evaluation:
Primary endpoints: Immunogenicity:

- Seroprotection status for anti-poliovirus type 1, 2 and 3 antibodies (antibody titer ≥ 8), anti-diphtheria antibodies (antibody concentration ≥ 0.1 IU/ml by ELISA, or diphtheria neutralising antibodies ≥ 0.016 IU/ml by VERO cell testing in subjects seronegative by ELISA testing one month after vaccination) and anti-tetanus antibodies (antibody concentration ≥ 0.1 IU/ml).
- Anti-PT, anti-PRN and anti-FHA antibody concentrations.

Secondary endpoints: Immunogenicity

- Seropositivity status for anti-PT, anti-FHA and anti-PRN antibodies (≥ 5 EL.U/ml), anti-mumps antibodies (≥ 231 U/ml), anti-measles antibodies (≥ 150 mIU/ml), anti-rubella antibodies (≥ 4 IU/ml and ≥ 10 IU/ml).
- Anti-poliovirus type 1, anti-poliovirus type 2 and anti-poliovirus type 3 antibody titers
- Anti-diphtheria toxoid, anti-tetanus toxoid, anti-measles, anti-mumps and anti-rubella antibody concentrations.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** INFANRIX®-IPV, PRIORIX™ **Name of active substance:** Diphtheria and tetanus toxoids, pertussis antigens (PT, FHA and PRN), poliovirus types 1, 2 and 3, Schwarz measles strain, RIT 4385 mumps strain, RA 27/3 rubella strain.	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

- Vaccine response to PT, PRN and FHA defined as appearance of antibodies in subjects who were initially (i.e. at pre-vaccination) seronegative or at least experienced a two-fold increase in antibody concentrations between pre and post-vaccination in subjects who were initially seropositive.

Safety and reactogenicity

- Occurrence of solicited local (pain, redness and swelling) and general (fever, irritability /fussiness, drowsiness and loss of appetite) symptoms during the 4-day follow-up period after vaccination.
- Occurrence of specific solicited general symptoms (fever, rash/exanthema, parotid/salivary gland swelling and any suspected signs of meningism including febrile convulsions) during the 15-day follow-up period after MMR vaccination.
- Occurrence of unsolicited symptoms during the 31-day follow-up period after vaccination.
- Occurrence of serious adverse events throughout the study period.

Statistical methods: Analysis was carried out on the vaccinated cohort and two ATP cohorts. The primary cohort for immunogenicity was the ATP immunogenicity cohort. As opposed to the protocol, the ATP safety cohort was primarily used for safety as it excluded the subjects with DTPw vaccine history that were erroneously enrolled in the study.

Analysis of demographics: Demographic characteristics (age in years, gender, race and vaccination history) were tabulated per group. The distribution of the subjects enrolled among study centers was also tabulated per group.

Analysis of immunogenicity:

Descriptive analysis: Seropositivity/ seroprotection rates to each vaccine antigen and their 95% confidence interval (CI) were tabulated for both groups. The Geometric mean concentration/ titers (GMC/GMTs) and their 95%CI were also calculated. The percentage of subjects with vaccine response to PT, FHA and PRN with their exact 95% CI, one month after vaccination was calculated for each group. Distribution of anti-diphtheria, anti-tetanus, anti-PT, anti-PRN, anti-FHA, anti-measles, anti-mumps and anti-rubella antibody concentrations and anti-poliovirus types 1, 2 and 3 antibody titers were displayed using reverse cumulative curves (RCCs), one month after vaccination.

Inferential analysis: The standardized asymptotic two-sided 95% CI for the group difference in seroprotection rates for anti-diphtheria, anti-tetanus and anti-poliovirus types 1, 2 and 3 antibodies, one month after vaccination, were calculated. The two-sided 95% CI for the ratio of GMCs for the pertussis antigens (anti-PT, anti-PRN and anti-FHA) between the two groups were computed using a one-way ANCOVA model on the logarithm10 transformation of the titers. The model included groups as fixed effect and pre-vaccination measurement as co-variable.

Exploratory analysis: The standardized asymptotic two-sided 95% CI for the group difference in the percentage of subjects showing vaccine response to PT, FHA and PRN, one month after vaccination were calculated. The two-sided 95% CI for the ratio of GMC/ GMTs for anti-diphtheria, anti-tetanus and anti-poliovirus types 1, 2 and 3 antibodies, anti-measles, anti-mumps and anti-rubella antibodies were computed using a one-way ANCOVA model on the logarithm10 transformation of the antibody concentrations/titers. The model included groups as fixed effect and pre-vaccination measurement as co-variable.

Analysis of safety: All safety analyses were descriptive.

Percentage (with exact 95% CI) of subjects reporting at least one local adverse event, at least one general adverse event (solicited or unsolicited) and any adverse event during the 4-day follow-up period after vaccination was calculated per group. The percentage (with exact 95% CI) of subjects reporting each solicited symptom was calculated by group over the solicited follow-up period.

The same calculations were done for each solicited local symptom rated as grade "2" or "3" in intensity, for each solicited symptom rated as grade "3" in intensity and for each solicited general symptoms assessed as related to vaccination. For each group, the percentage of subjects reporting each MMR

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium Name of Finished Product: INFANRIX®-IPV, PRIORIX™ Name of active substance: Diphtheria and tetanus toxoids, pertussis antigens (PT, FHA and PRN), poliovirus types 1, 2 and 3, Schwarz measles strain, RIT 4385 mumps strain, RA 27/3 rubella strain.	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

specific solicited general symptom, with a reasonable possibility to be related to vaccination and with a grade "3" intensity over the 15-day follow-up period was tabulated along with exact 95% CIs.
Percentage of subjects reporting unsolicited symptoms and those with causal relationship to vaccination, classified by WHO Preferred Terms, during the 31-day follow-up period after vaccination were tabulated with its 95% CI. Percentage of subjects receiving concomitant medication (any medications, antipyretics, and prophylactic antipyretics) during the 4-day and 31-day follow-up period after vaccination was tabulated by group.

SUMMARY-CONCLUSIONS:

Demography: The mean age of the ATP immunogenicity cohort at the time of vaccination was four years with a standard deviation of 0.2 years. The female to male ratio was 1.26. The majority of subjects (97.6%) in both groups were white.

Immunogenicity: The primary analysis was done on the ATP immunogenicity cohort.
Prior to booster vaccination, seroprotection and seropositivity rates were similarly high in the two groups. One month after vaccination, all subjects in both groups had seroprotective antibody levels against diphtheria, tetanus, poliovirus types 1, 2 and 3 antigens and majority of subjects showed vaccine response to all three pertussis antigens (PT, FHA and PRN). Despite the initial high seroprotection and seropositivity rates, marked increases in post-vaccination GMC/GMTs were observed.
The upper limit of the asymptotic two-sided 95% CI for the difference in seroprotection rates and ratio of GMCs as defined above were below the pre-defined clinical limit for non-inferiority. Therefore, it can be concluded that the DTaP-IPV vaccine is non-inferior to DTaP and IPV vaccines administered separately in terms of seroprotection to diphtheria, tetanus, each of the polio serotypes and in terms of anti-PT, anti-FHA and anti-PRN antibody concentrations *(Amended 7 October 2004)*.
The exploratory analysis on GMC ratios is also consistent with the similarity of the reponse in the two groups.

Table 1. Differences in seroprotection/vaccine response (for pertussis antigens) rates one month after booster vaccination, with their asymptotic 95% CIs (ATP immunogenicity cohort)

Endpoints	Group DTaP-IPV + MMR		Group DTaP + IPV + MMR		DTaP + IPV + MMR minus DTaP-IPV + MMR		
	N	%	N	%	Difference	95% CI LL	95% CI UL
Anti-diphtheria ≥ 0.1 IU/ml	165	100.0	159	100.0	0.0	-2.4	2.3*
Anti-tetanus ≥ 0.1 IU/ml	165	100.0	159	100.0	0.0	-2.3	2.4*
Anti-PT (2 fold increase)	159	98.7	148	99.3	0.6	-1.8	3.1
Anti-FHA (2 fold increase)	159	96.9	148	99.3	2.5	-0.2	5.7
Anti-PRN (2 fold increase)	159	98.1	150	100.0	1.9	0.1	4.6
Anti-poliovirus type 1 ≥ 8	156	100.0	151	100.0	0.0	-2.5	2.4*
Anti-poliovirus type 2 ≥ 8	153	100.0	152	100.0	0.0	-2.5	2.4*
Anti-poliovirus type 3 ≥ 8	148	100.0	147	100.0	0.0	-2.5	2.5*

N: number of subjects with available data
%: percentage of subjects with seroprotective antibody levels post-vaccination
Difference: Difference between the two groups in percentage of seroprotected subjects (Group DTaP + IPV + MMR minus Group DTaP-IPV + MMR)
95% CI: Standardised asymptotic two-sided 95% confidence interval; LL: Lower Limit; UL: Upper Limit
* Upper limit of 95% CI below the pre-specified clinical limit of non-inferiority (10%) for difference in seroprotection rates. 95% CI for the differences in vaccine response were exploratory evaluations

Document 1

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** INFANRIX®-IPV, PRIORIX™ **Name of active substance:** Diphtheria and tetanus toxoids, pertussis antigens (PT, FHA and PRN), poliovirus types 1, 2 and 3, Schwarz measles strain, RIT 4385 mumps strain, RA 27/3 rubella strain.	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Table 2: Ratios of GMC/T's one month after booster vaccination, with their 95% CIs (ATP immunogenicity cohort)

Antibody	Group DTaP-IPV + MMR		Group DTaP + IPV + MMR		DTaP + IPV + MMR over DTaP-IPV + MMR		
	N	GMC/T	N	GMC/T	Ratio	95%CI	
						LL	UL
Anti-diphtheria	159	6.220	150	5.859	0.942	0.796	1.115
Anti-tetanus	159	8.222	150	6.644	0.808	0.714	0.914
Anti-PT	159	112.71	148	128.34	1.139	0.950	1.365*
Anti-FHA	159	360.29	148	429.72	1.193	1.030	1.382*
Anti-PRN	159	703.80	150	676.11	0.961	0.819	1.127*
Anti-poliovirus type 1	145	2985.66	142	3258.44	1.091	0.877	1.358
Anti-poliovirus type 2	142	3012.87	143	3514.47	1.166	0.950	1.433
Anti-poliovirus type 3	138	4898.58	137	4813.27	0.983	0.815	1.184
Anti-measles	163	2657.54	161	2579.88	0.971	0.865	1.090
Anti-mumps	153	2446.70	158	2243.26	0.917	0.808	1.040
Anti-rubella	163	140.57	162	155.81	1.108	1.009	1.217

N: number of subjects with pre- and post-vaccination results
Ratio: ratio between the two groups in terms of GMC/Ts (DTaP + IPV + MMR over DtaP-IPV + MMR)
GMC/T: Geometric Mean Concentrations/Titers adjusted for baseline concentration
95% CI: Two-sided 95% confidence interval; LL: Lower Limit; UL: Upper Limit
*Upper limit of 95% CI below the pre-specified clinical limit of non-inferiority (1.5) for GMC/T ratios. 95% CI for GMC/T ratios for other antigens were exploratory evaluations.

Table 3: Seropositivity rates and GMCs after MMR booster vaccination, one month after the booster dose (ATP immunogenicity cohort)

Antibodies	Group DTaP-IPV + MMR							Group DTaP + IPV + MMR						
	N	S+(%)	95%CI		GMC	95%CI		N	S+ (%)	95%CI		GMC	95%CI	
			LL	UL		LL	UL			LL	UL		LL	UL
Anti-mumps	153	100.0	97.6	100.0	2437.7	2159.5	2751.6	158	100.0	97.7	100.0	2251.3	2037.6	2487.5
Anti-measles	163	100.0	97.8	100.0	2549.9	2236.6	2907.2	161	99.4	96.6	100.0	2690.1	2379.7	3041.0
Anti-rubella	163	100.0	97.8	100.0	139.7	128.5	151.9	162	100.0	97.7	100.0	156.8	146.2	168.1

N: number of subjects with available results
GMC: Geometric mean concentrations
S+: Antibody concentration ≥ assay cut-off (cut-off for mumps: 231 U/ml, measles: 150 mIU/ml, rubella: 4 IU/ml)
%: Percentage of seropositive subjects
95% CI: 95% confidence interval; LL: Lower Limit; UL: Upper Limit

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** INFANRIX®-IPV, PRIORIX™ **Name of active substance:** Diphtheria and tetanus toxoids, pertussis antigens (PT, FHA and PRN), poliovirus types 1, 2 and 3, Schwarz measles strain, RIT 4385 mumps strain, RA 27/3 rubella strain.	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

The immune response to the concomitantly administered MMR vaccine was in line with previously reported responses to a second dose of this vaccine.

Safety: Primary analysis was done on the ATP safety cohort.

Table 4: Incidence of solicited local and general symptoms for the ATP safety cohort

		Group DTaP-IPV + MMR (N = 171)				Group DTaP + IPV + MMR (N = 167)			
		n	%	95%CI LL	95%CI UL	n	%	95%CI LL	95%CI UL
Solicited local symptoms (Day 0 to Day 3 post-vaccination)									
Pain	Any	139	81.3	74.6	86.8	126	75.4	68.2	81.8
	Grade "3"	12	7.0	3.7	11.9	8	4.8	2.1	9.2
Redness	Any	138	80.7	74.0	86.3	149	89.2	83.5	93.5
	> 50 mm	56	32.7	25.8	40.3	70	41.9	34.3	49.8
Swelling	Any	106	62.0	54.3	69.3	126	75.4	68.2	81.8
	> 50 mm	41	24.0	17.8	31.1	47	28.1	21.5	35.6
Solicited general symptoms (Day 0 to Day 3 post-vaccination)									
Drowsiness	Any	40	23.4	17.3	30.5	40	24.0	17.7	31.2
	Grade "3"	5	2.9	1.0	6.7	3	1.8	0.4	5.2
Fever (axillary temperature)	Any	39	22.8	16.7	29.8	45	26.9	20.4	34.3
	> 39.0 °C	3	1.8	0.4	5.0	1	0.6	0.0	3.3
Irritability	Any	45	26.3	19.9	33.6	55	32.9	25.9	40.6
	Grade "3"	2	1.2	0.1	4.2	0	0.0	0.0	2.2
Loss of appetite	Any	35	20.5	14.7	27.3	40	24.0	17.7	31.2
	Grade "3"	4	2.3	0.6	5.9	3	1.8	0.4	5.2

N: Number of subjects having received at least one dose

n (%): Number (percentage) of subjects reporting a general or local symptom

Any site: n: Number of subjects presenting at least one local symptom whatever the number of injections.

Grade "3" symptoms: Symptoms that prevented normal daily activities

There was no difference between groups in terms of the incidence and intensity of solicited local and general symptoms. Solicited general symptoms of grade "3" intensity were uncommon (< 3%).

During the 15-day follow-up period after vaccination, the incidence of fever was similar in the two groups, with temperature > 39.0 °C reported for 4.1% and 5.4% of study subjects in the two groups. A similar proportion of subjects (21.6% and 20.4%) received antipyretics during the course of the study.

With respect to solicited symptoms specific to MMR vaccination, rash causally related to MMR vaccination was reported for 11 subjects in total. No cases of meningism were reported.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** INFANRIX®-IPV, PRIORIX™ **Name of active substance:** Diphtheria and tetanus toxoids, pertussis antigens (PT, FHA and PRN), poliovirus types 1, 2 and 3, Schwarz measles strain, RIT 4385 mumps strain, RA 27/3 rubella strain.	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Table 5: Large injection site swelling and extent of the reaction for the ATP safety cohort

	DTaP-IPV (N = 171)		DTaP (N = 167)	
	n	%	n	%
Any large injection site swelling	42	24.56	49	29.34
Local > 50mm	31	18.13	30	17.96
Diffuse not involving adjacent joint	1	0.58	9	5.39
Involving at least one adjacent joint	10	5.85	10	5.99
• *Extending above the shoulder*	*4*	*2.34*	*2*	*1.19*
• *Upper arm swelling*	*2*	*1.17*	*2*	*1.19*
• *Whole-limb swelling*	*0*	*0.0*	*0*	*0.0*

N: Number of subjects having received at least one dose
n (%): Number (percentage) of subjects with a report of the symptom
Extending above the shoulder: Swelling extending past the shoulder joint, limited to the shoulder area.
Upper arm swelling: Swelling from the shoulder to the elbow (including both joints)
Whole-limb swelling: Swelling from the shoulder to the hand
Note: Symptoms in italics are a sub-classification of large swelling reactions involving at least one adjacent joint

Large swelling reactions at the site of injection of the DTaP based vaccine were reported for a similar percentage of subjects in the two groups. The majority of these swelling reactions were locally limited. In each group, ten subjects reported a reaction that involved the adjacent joint, i.e. the shoulder. Given that the vaccines were injected in the deltoid, this is not unexpected. Indeed, half of these reactions were limited to the shoulder area, with no further extension. For the other half, six extended above the shoulder with no further extension towards the elbow and four involved both the shoulder and the elbow joints. Only 2 subjects (DTaP-IPV vaccinees) reported functional impairment that prevented normal everyday activities. Large swellings occurred within 2 days post-vaccination and lasted less than 5 days for the majority of cases.

Unsolicited symptoms: During the 31-day follow-up period after vaccination, the incidence of grade "3" unsolicited symptoms was similar in both groups. In the DTaP + IPV + MMR group, a larger percentage of subjects reported unsolicited injection site reactions and rhinitis determined by the investigator to be causally related to vaccination.

Serious adverse events (SAE): One subject (n° 420 in Group DTaP + IPV + MMR) reported an SAE, which was considered by the investigator to be causally related to vaccination. Three days after the vaccination, the subject developed high fever (40 °C) and headache. The next day he became lethargic and suffered from severe headache and loss of appetite. He was hospitalized, diagnosed with significant fever without infective focus and discharged from hospital. He was reviewed for persistent fever five days later and a diagnosis of concurrent non-serious bronchitis was made. The subject was treated with antibiotics and had recovered one week later.

There were no dropouts due to SAEs.

Document 1

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** INFANRIX®-IPV, PRIORIX™ **Name of active substance:** Diphtheria and tetanus toxoids, pertussis antigens (PT, FHA and PRN), poliovirus types 1, 2 and 3, Schwarz measles strain, RIT 4385 mumps strain, RA 27/3 rubella strain.	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Conclusions:

- GSK Biologicals' DTaP-IPV vaccine was immunogenic as a booster dose in children 4 to 6 years of age, previously vaccinated with three doses of DTaP and IPV or OPV vaccine during the first year of life and a booster dose of DTaP vaccine in the second year of life.
- The non-inferiority of the combined DTaP-IPV vaccine compared to separately administered DTaP and IPV was demonstrated in terms of immune response to each component antigen.
- The response to the concomitantly administered MMR vaccine was similar in the two groups and similar to previously reported responses for a second dose of this vaccine.
- No differences in the incidence and intensity of solicited symptoms were observed following vaccination with either DTaP-IPV + MMR or separately administered DTaP, IPV and MMR. Local reactions were observed more frequently than general symptoms and grade "3" general symptoms were rare.
- A similar incidence of large swelling reactions was observed after DTaP-IPV or DTaP booster vaccination. Incidences were within the range published for a fifth dose of DTaP vaccine at pre-school age. Upper arm swelling i.e. large injection site swellings involving both the shoulder and elbow joints occurred in 1.2% of the subjects.

Date of report: 5 March 2004 (Final)
Date of amendment: 7 October 2004

Document 1

Name of Company: SmithKline Beecham Biologicals, Rixensart, Belgium **Name of Finished Product:** **Name of active substance:** DTPa, HBV, IPV, Hib	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Title of the study : 217744/058 (DTPa-HBV-IPV-058)
Open, randomised, multicentre, phase III clinical trial to assess and to compare the reactogenicity of a booster dose of SB Biologicals' DTPa-HBV-IPV and Hib conjugate vaccines when mixed extemporaneously and administered in a single injection and of SB Biologicals' DTPa-IPV/Hib with or without *Engerix-B ™* vaccines administered in separate injections in 12 to 18 months old healthy children, previously vaccinated at the age of 3, 4 and 5 months in primary vaccination study DTPa-HBV-IPV-039 (217744/039).

Principal Investigator: s22 s22
Kinderklinik Johannes-Gutenberg-Universität, Langenbeckstraße 1, 55101 Mainz, Germany

Study Center(s): 83 sites in Germany

Publication (reference): Not published as of July 10, 2000

Study period:	Date of first visit: August 13, 1999 Date of last visit: March13, 2000	**Clinical phase:** III

Objectives:
Primary:
To demonstrate that SB Biologicals' DTPa-HBV-IPV vaccine mixed with SB Biologicals' Hib conjugate vaccine, and administered in a single injection, is at least as safe as SB Biologicals' DTPa-IPV/Hib and SB Biologicals' HBV vaccines administered in two separate injections, in terms of incidence of grade 3 solicited symptoms after booster vaccination.

Secondary:
- To assess the safety of SB Biologicals' DTPa-HBV-IPV vaccine mixed with SB Biologicals' Hib conjugate vaccine and administered in a single injection, and compare it with the safety of SB Biologicals' DTPa-IPV/Hib vaccine in terms of incidence of grade 3 solicited symptoms after booster vaccination.
- To assess the safety and reactogenicity of the study vaccines in terms of occurrence of solicited and unsolicited symptoms, and of occurrence of serious adverse events after booster vaccination.

Methodology:
Study design: Open, randomised booster study with three groups in a 3:1:1 ratio:
Group 1: one single injection of SB's DTPa-HBV-IPV vaccine mixed with SB's Hib conjugate vaccine (modified formulation)
Group 2: one single injection of SB's DTPa-IPV/Hib vaccine (in Germany: *Infanrix ™-IPV+Hib*)
Group 3: two separate injections of SB's DTPa-IPV/Hib (in Germany: *Infanrix™-IPV+Hib*) and SB's HBV (in Germany: *Engerix-B ™ Kinder*) vaccines.
Subjects received 1 vaccine dose (1 or 2 injections, depending on their group) at 12 to 18 months of age. No blood samples were taken.
(Note: subjects were primed with either SB's DTPa-HBV-IPV/Hib or DTPa-IPV/Hib and HBV vaccines in study DTPa-HBV-IPV-039 (217744/039), using a 3:1 randomisation ratio.)

Number of subjects:
Enrolled: 1149 Completed: 1145
According-tot-protocol (ATP) cohort for safety: 1138 (Group 1= 688; Group 2= 223; Group 3= 227)

Diagnosis and criteria for inclusion:
Healthy male or female between 12 and 18 months of age at the time of booster vaccination who had received a complete primary vaccination course of DTPa-HBV-IPV vaccine mixed with the Hib conjugate vaccine, or DTPa-IPV/Hib and HBV in study DTPa-HBV-IPV-039 (217744/039).

Document 1

Name of Company: SmithKline Beecham Biologicals, Rixensart, Belgium **Name of Finished Product:** **Name of active substance:** DTPa, HBV, IPV, Hib	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Test product, dose, mode of administration, lot No.:

- SB's liquid combined **DTPa-HBV-IPV vaccine**, containing per 0.5 ml dose: ≥30 IU (25 Lf), Diphtheria toxoid; ≥40 IU (10 Lf), Tetanus toxoid; 25 mcg pertussis toxoid (PT); 25 mcg filamentous haemagglutinin (FHA); 8 mcg pertactin (PRN); 10 mcg HBsAg (recombinant), 40D antigen units Polio virus type 1 (Mahoney), 8D antigen units Polio virus type 2 (MEF-1), 32D antigen units Polio virus type 3 (Saukett), ≤ 2.5 mg Phenoxyethanol, 0.7 mg aluminium. Lot number D21799B2 was used.
- SB's lyophilized ***Haemophilus influenzae* type B conjugate vaccine (modified formulation)**, containing per 0.5 ml dose: 10 mcg Polyribosyl Ribitol Phosphate (PRP), 20-40 mcg Tetanus toxoid, 0.12 mg aluminium, 10 mg Lactose. Lot number Dhib200A41 was used. This Hib vaccine was reconstituted with the liquid DTPa-HBV-IPV vaccine and injected intramuscularly into the left anterolateral thigh.

Reference therapy, dose, mode of administration, lot number:

- SB's **DTPa-IPV vaccine** containing per dose of 0.5 ml: 25 mcg PT, 25 mcg FHA, 8 mcg PRN, ≥ 30 IU (25 Lf) Diphtheria toxoid, ≥ 40 IU (10 Lf) Tetanus toxoid, 40 D antigen units Poliovirus type 1 (Mahoney), 8 D antigen units Poliovirus type 2 (MEF-1), 32D antigen units Poliovirus type 3 (Saukett), 0.5 mg Aluminium, ≤ 2.5 mg Phenoxyethanol, Lot 20742A9A was used.
- SB's lyophilized ***Haemophilus influenzae* type B conjugate vaccine (Hiberix™)** containing per dose of 0.5 ml: 10 mcg PRP, 20-40 mcg Tetanus toxoid and 10 mg Lactose. Lot Hib248A47A was used. Hiberix™ was reconstituted with DTPa-IPV and injected intramuscularly into the left anterolateral thigh. This combined vaccine is commercially available in Germany as Infanrix™-IPV+Hib.
- SB's **hepatitis B vaccine (Engerix-B™-Kinder)** containing per dose of 0.5 ml: 10 mcg HBsAg (recombinant), 1:20,000Thiomersal, 0.49 mg Disodium phosphate dihydrate, 0.355 mg Disodium dihydrogen phosphate dihydrate, 0.25 mg Aluminium and 150 mM Sodium chloride. Lot ENG2830F9 was used. This vaccine was injected intramuscularly into the right anterolateral thigh.

Duration of treatment: Approximately 1 month for each subject.

Criteria for evaluation:

Safety: Assessment of solicited local symptoms (pain, redness and swelling at the injection site) and general symptoms (fever, irritability/fussiness, drowsiness and loss of appetite) during a four-day follow-up period after vaccination. Recording of unsolicited symptoms during a 30-day follow-up period after vaccination and of serious adverse events (SAE) during the entire study period. The primary end point was the occurrence of grade 3 solicited symptoms within 4 days after booster vaccination.

Statistical methods:

Safety: The percentage of subjects reporting symptoms within the 4 days following vaccination and their exact 95% confidence interval (CI) were computed by group according to the type of symptoms, their intensity and relationship to vaccination. The difference between the DTPa-HBV-IPV/Hib vaccine (group 1) and the control DTPa-IPV/Hib + HBV vaccines (group 3) in terms of the incidence of grade 3 solicited symptoms within the 4-days follow-up period after booster vaccination, was computed with its exact 90% CI (Stat Xact, difference between proportions). The primary objective was demonstrated if the upper limit of the 90% CI was below the pre-defined 10% limit defining clinical non-inferiority.

The difference between the DTPa-HBV-IPV/Hib vaccine (group 1) and the DTPa-IPV/Hib vaccine without co-administration of HBV (group 2) was evaluated using the same approach and the same pre-defined clinical limit defining non-inferiority of 10%.

The percentage of subjects reporting unsolicited symptoms within 30 days following booster vaccination was tabulated according to the WHO preferred term and according to the relationship to vaccination. SAEs were described.

Document 1

Name of Company: SmithKline Beecham Biologicals, Rixensart, Belgium **Name of Finished Product:** **Name of active substance:** DTPa, HBV, IPV, Hib	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

SUMMARY-CONCLUSIONS :

Demography: The mean age of the booster cohort was 15.3 months. Ninety-five percent of the study population was white and the racial distribution was comparable between the groups. The percentage of male and female subjects was similar (51% male and 49% female) between the groups.
Safety Results: Redness at the injection site was the most commonly reported solicited local symptom during the four-day follow-up period. Fever and irritability were the most frequently reported solicited general symptoms. Redness and swelling >20 mm were the most commonly reported grade 3 symptoms. Most local and general solicited symptoms were of grade 1 or 2 intensity

Table 1: *Incidence of any symptoms and grade 3 solicited symptoms - ATP cohort*

	Group 1 DTPa-HBV-IPV/Hib (N= 685*)			Group 2 DTPa-IPV/Hib (N= 221)			Group 3 DTPa-IPV/Hib + HBV (N= 227)		
Symptom	**%**	**95%CI**		**%**	**95%CI**		**%**	**95%CI**	
Any symptom	73.6	70.1	76.9	73.8	67.4	79.4	71.8	65.5	77.6
Grade 3	20.8	17.9	24.1	24.9	19.3	31.1	14.5	10.2	19.8
Any local	54.9	51.1	58.7	52.5	45.7	59.2	52.0	45.3	58.6
Grade 3	16.8	14.1	19.8	18.6	13.7	24.3	11.9	8.0	16.8
Pain	31.2	27.8	34.9	29.4	23.5	35.9	33.0	27.0	39.6
Grade 3	6.4	4.7	8.5	4.5	2.2	8.2	3.1	1.2	6.3
Redness	48.2	44.4	52.0	43.4	36.8	50.3	42.7	36.2	49.4
>20 mm	8.8	6.8	11.1	10.9	7.1	15.7	6.2	3.4	10.1
Swelling	30.7	27.2	34.3	27.1	21.4	33.5	27.3	21.6	33.6
>20 mm	8.6	6.6	11.0	11.8	7.8	16.8	7.5	4.4	11.7
Any general	63.0	59.2	66.6	64.7	58.0	71.0	59.9	53.2	66.3
Grade 3	6.9	5.1	9.0	9.0	5.6	13.6	3.5	1.5	6.8
Fever ≥38.0°C	42.2	38.5	46.0	40.7	34.2	47.5	34.8	28.6	41.4
>39.5°C	3.2	2.0	4.8	4.1	1.9	7.6	1.8	0.5	4.5
Drowsiness	33.7	30.2	37.4	33.0	26.9	39.7	30.4	24.5	36.8
Grade 3	2.0	1.1	3.4	1.4	0.3	3.9	1.3	0.3	3.8
Irritability	34.7	31.2	38.4	39.8	33.3	46.6	30.8	24.9	37.3
Grade 3	2.2	1.2	3.6	5.0	2.5	8.7	0.9	0.1	3.1
Loss of Appetite	28.5	25.1	32.0	26.7	21.0	33.0	24.2	18.8	30.3
Grade 3	1.6	0.8	2.9	1.4	0.3	3.9	0.9	0.1	3.1

N = number of subjects with at least one symptom sheet completed (solicited symptoms only)

* For any symptom, any local symptom and any general symptom calculations, N includes subjects with at least one documented dose (includes both solicited and unsolicited symptoms); as a consequence, N = 686 for group 1 for these calculations (no change for group 2 and group 3).
% = percentage of subjects reporting a specified symptom; 95% CI = Exact 95% confidence interval
Grade 3 pain = cries when the limb is moved/spontaneously painful; Grade 3 drowsiness = drowsiness that prevents normal activity;
Grade 3 irritability = crying or protesting that cannot be comforted / prevents normal activity;
Grade 3 loss of appetite = Not eating at all

Name of Company: SmithKline Beecham Biologicals, Rixensart, Belgium Name of Finished Product: Name of active substance: DTPa, HBV, IPV, Hib	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

Table 2 presents the exact 90% CI for the difference between DTPa-HBV-IPV/Hib and (minus) the groups 2 and 3 for the percentage of subjects with any grade 3 solicited symptoms within 4 days after vaccination.

Table 2: Difference between group 1 and each of groups 2 and 3 in terms percentage of subjects with any grade 3 solicited symptoms after vaccination (ATP cohort for safety)

N	Rate (%)	N	Rate(%)	Difference (%)	90% CI	
Group 1		Group 3		(Group 1 minus Group 3)		
686	20.85	227	14.54	6.31	0.99	11.36
Group 1		Group 2		(Group 1 minus Group 2)		
686	20.85	221	24.89	-4.04	-10.45	1.55*

Group 1: DTPa-HBV-IPV/Hib; **Group 2:** DTPa-IPV/Hib; **Group 3:** DTPa-IPV/Hib + HBV
N: Number of subjects with at least one symptom sheet completed
Rate (%): percentage of subjects experiencing any grade 3 solicited symptom during the 4-day follow-up period after vaccination
90% CI = Exact 90% confidence interval
*: Upper limit below the 10% clinical limit of non-inferiority

Although the absolute difference between DTPa-HBV-IPV/Hib and DTPa-IPV/Hib + HBV was only 6.3%, the upper limit of the 90% CI for the difference exceeded the predefined clinical limit of 10% and therefore the primary objective was not reached. However, the upper limit of the 90% CI for the difference between groups 1 and 2 did not exceed the predefined clinical limit, suggesting that a booster dose of DTPa-HBV-IPV/Hib is not more reactogenic than a booster dose of DTPa-IPV/Hib when administered without concomitant administration of HBV.

Unsolicited symptoms were reported by at least 40% of all subjects (40% of group 1 subjects, 43% of group 2 subjects and 37% of group 3 subjects). 10.5% of the unsolicited symptoms were assessed as probably or suspected to be related to vaccination

Serious Adverse Events: 7 subjects reported SAEs (n° 155, 496, 762, 954 and 1058 from group 1, n° 607 from group 2 and n° 345 from group 3). All were assessed as not related to vaccination.One subject (n° 607) dropped out of the study due to an SAE (fever 26 days after vaccination, with seizures and aspiration). All other subjects had recovered by the time of study conclusion.

Conclusion(s):

- The incidence of grade 3 symptoms was similarly reported following a booster dose of DTPa-HBV-IPV/Hib and a booster dose of DTPa-IPV/Hib in the second year of life.
- Although unusual, the incidence of symptoms reported in the group receiving 2 injections (DTPa-IPV/Hib and HBV) was lower than that which was reported for the group receiving DTPa-IPV/Hib without concomitant administration of HBV. Therefore the difference observed between DTPa-HBV-IPV/Hib and DTPa-IPV/Hib + HBV should be interpreted with caution.

July 3, 2000 SmithKline Beecham Biologicals' Document 1
Final Study Report 217744/059 (DTPa-HBV-IPV-059)
Confidential and Proprietary Information

Name of Company: SmithKline Beecham Biologicals, Rixensart, Belgium **Name of Finished Product:** **Name of active substance:** DTPa-HBV-IPV/ Hib	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Title of the study : 217744/059 (DTPa-HBV-IPV-059)
Open, multicentre, phase III clinical trial to assess the immunogenicity and reactogenicity of SB Biologicals' DTPa-HBV-IPV and Hib conjugate vaccines when mixed extemporaneously and administered in a single injection as a booster dose to 12 to 18 months old healthy children, previously vaccinated at the age of 3, 4 and 5 months in primary vaccination study DTPa-HBV-IPV-048 (217744/048), with either three doses of the same vaccines or with three doses of DTPa-IPV/Hib and *Engerix-B*™ vaccines administered in separate injections.

Principal Investigator: s22 [redacted]

Study Center(s): Paediatrische Infektiologie und Vakzinologie
Universitäts-Kinderspital beider Basel
Römergrasse 8
Postfach CH-4005 Basel

Publication (reference): Not published as of July 3, 2000

Study period: Date of first visit: July 6, 1999. Date of last visit: February 4, 2000.	**Clinical phase: III**

Objectives:
Primary:
To assess the immunogenicity in terms of anti-PRP antibody titres ≥1.0 µg/ml one-month after a booster dose of SB Biologicals' modified Hib conjugate vaccine when mixed extemporaneously and administered in the same syringe with SB Biologicals' combined DTPa-HBV-IPV vaccine.
Secondary:
- To assess the immune response in terms of seroprotection/seropositivity rates and antibody titres against all vaccine antigens one month after a booster dose of SB Biologicals' modified Hib conjugate vaccine when mixed extemporaneously and administered in the same syringe with SB Biologicals' combined DTPa-HBV-IPV vaccine.
- To assess the persistence of antibodies to all antigens given during the three-dose primary vaccination course (PRP, diphtheria and tetanus toxoids, PT, FHA, PRN, HBsAg, Polio type 1, 2 and 3), expressed as pre-booster antibody titres and seroprotection/seropositivity rates.
- To assess the safety and reactogenicity of the study vaccines in terms of percentage of subjects in each group with solicited, unsolicited and serious adverse events after the booster dose.

Methodology:
Study design: Open booster study with all subjects receiving the same booster vaccine. For the persistence and reactogenicity results, subjects were divided into two subgroups based on their primary vaccination:
Group P1 : DTPa-HBV-IPV/Hib primed and DTPa-HBV-IPV/Hib boosted
Group P2 : DTPa-IPV/Hib + HBV primed and DTPa-HBV-IPV/Hib boosted
Blood samples were taken prior to and one month after the booster dose.

Number of subjects:
Planned: 500
Enrolled: 443 (Group P1 = 341; Group P2 = 102) Completed: 439
Analysed for According-to-protocol (ATP) safety: 440 (Group P1 = 338; Group P2 = 102)
Analysed for ATP immunogenicity: 398 (Group P1 = 307; Group P2 = 91)

Doc ID 1.2

Name of Company: SmithKline Beecham Biologicals, Rixensart, Belgium **Name of Finished Product:** **Name of active substance:** DTPa-HBV-IPV/ Hib	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Diagnosis and criteria for inclusion:
Healthy subjects between 12 and 18 months of age at the time of the booster vaccination who had received a complete primary vaccination course with DTPa-HBV-IPV/ Hib (modified formulation), or DTPa-IPV/Hib + HBV in the study DTPa-HBV-IPV-048 (217744/048). The subjects were to be in good clinical condition at the time of enrollment with no history of diphtheria, tetanus, pertussis, polio, hepatitis B and/or Hib booster vaccination or disease. Written informed consent was to be obtained from the parents or guardians of the subject prior to entry into the study.

Test product, dose, mode of administration, lot No.:
Vaccination schedule/site:

Subgroup	Visit	Vaccination	Route	Site
P1 & P2	1	DTPa-HBV-IPV mixed with Hib (modified formulation)	Intramuscular	Left Thigh

Vaccine/composition/dose/lot number:

- One dose (0.5 ml) of the **combined diphtheria, tetanus, tricomponent acellular pertussis, hepatitis B, enhanced potency inactivated polio (DTPa-HBV-IPV) vaccine** contained: ≥30 IU (25 Lf) diphtheria toxoid, ≥40 IU (10 Lf) tetanus toxoid, 25 mcg pertussis toxoid (PT), 25 mcg filamentous haemaglutinin (FHA), 8 mcg pertactin (PRN), 10 mcg HBsAg (recombinant), 40D antigen units polio virus type 1 (Mahoney strain), 8D antigen units polio virus type 2 (MEF-1 strain), 32D antigen units polio virus type 3 (Saukett strain), 0.7 mg aluminium and ≤2.5 mg phenoxyethanol. Lot number = D21799B2
- One dose (0.5 ml after reconstitution) of ***Haemophilus influenzae*** **type b conjugate vaccine** contained: 10 mcg Polyribosyl Ribitol Phosphate (PRP), 20-40 mcg Tetanus toxoid, 0.12 mg aluminium and 10 mg lactose. Lot Number = Dhib200A41.

Duration of treatment: Approximately one month for each subject.

Reference therapy: Not Applicable

Criteria for evaluation:
Immunogenicity:
Measurement of antibody titre against each vaccine antigen, prior to the booster dose and approximately one month after.
The primary endpoint was the percentage of subjects with anti-PRP ≥1.0 mcg/ml one month after the booster dose. The secondary endpoints were seroprotection rates to D, T, HBsAg, and poliovirus (Types 1, 2, 3), seropositivity and vaccine response rates for the pertussis components (PT, FHA, and PRN) and geometric mean titres (GMT) for antibodies against all vaccine antigens.

Safety:
Recording of solicited local (redness, swelling and pain at the injection site) and general (fever, drowsiness, irritability and loss of appetite) symptoms by the parents/guardians during a 4 day follow-up period after vaccination. Recording of unsolicited adverse events, including serious adverse events (SAE) during the whole study period up to 30 days after the study vaccine administration.

Statistical methods:
The analysis was performed according to protocol.

Immunogenicity: Immunogenicity before and after vaccination was evaluated for all antigens in terms of GMTs and seropositivity/seroprotection rates with their 95% confidence intervals (CIs). Vaccine response rates to the pertussis antigens after vaccination were also calculated with their exact 95% CIs. Results were shown by priming group and overall. Immunogenicity before vaccination was also analyzed by primary vaccine group for the purpose of antibody

Name of Company: SmithKline Beecham Biologicals, Rixensart, Belgium **Name of Finished Product:** **Name of active substance:** DTPa-HBV-IPV/ Hib	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

persistence evaluation.

Reactogenicity and safety: the percentage of subjects reporting any symptom within the 4 days following vaccination and their exact 95% CI were computed by priming group and overall according to the type of symptoms, their intensity and relationship to vaccination. The percentage of subjects reporting any unsolicited symptoms within 30 days following vaccination and their exact 95% CI were computed by priming group and overall after classification by WHO preferred term. SAEs were described.

SUMMARY CONCLUSIONS:

Demographics: The mean age of the Total cohort was 14.4 months at the time of booster vaccination. The percentage of male and female subjects was similar (52.6% male and 47.4% female) in the Total cohort.

Immunogenicity results:

Primary immunogenicity analyses were based on the ATP cohort.

Pre-booster antibody persistence:

Table 1: Percentage of seropositive/seroprotected subjects and GMTs prior to booster vaccination (ATP cohort for antibody persistence)

Antibody Cut-off	Group	%	95% CI		GMT	95% CI	
Anti-PRP ≥ 0.15 mcg/ml	P1	83.8	79.4	87.7	0.53	0.46	0.62
	P2	78.4	68.8	86.1	0.46	0.36	0.60
Anti-Diphtheria ≥ 0.016 IU/ml*	P1	99.4	98.5	100	0.13	0.11	0.14
	P2	96.9	93.5	100	0.11	0.09	0.14
Anti-Tetanus ≥ 0.1 IU/ml	P1	89.4	85.6	92.5	0.28	0.25	0.31
	P2	83.7	74.8	90.4	0.23	0.20	0.28
Anti-PT ≥ 5 EL.U/ml	P1	75.4	70.4	79.9	8.2	7.4	9.0
	P2	56.1	45.7	66.1	5.7	4.8	6.7
Anti-FHA ≥ 5 EL.U/ml	P1	99.7	98.3	100.0	38.6	35.3	42.3
	P2	99.0	94.3	100.0	32.7	27.9	38.4
Anti-PRN ≥ 5 EL.U/ml	P1	88.5	84.6	91.7	17.6	15.6	19.7
	P2	94.9	88.6	98.3	17.9	15.0	21.4
Anti-HBs ≥ 10 mIU/ml	P1	96.7	94.1	98.3	148.5	128.4	171.8
	P2	86.7	78.4	92.7	94.6	67.0	133.5
Anti-Polio 1 ≥ 8	P1	93.4	90.0	95.9	67.0	57.0	78.7
	P2	91.8	83.8	96.6	54.0	41.5	70.3
Anti-Polio 2 ≥ 8	P1	92.3	88.6	95.0	47.7	40.8	55.7
	P2	94.0	86.5	98.0	44.6	35.0	56.7
Anti-Polio 3 ≥ 8	P1	98.7	96.7	99.6	128.3	111.3	147.9
	P2	96.5	90.0	99.3	102.5	80.0	131.3

Group P1: DTPa-HBV-IPV/Hib primed (N= 331 for ATP cohort for antibody persistence)
Group P2: DTPa-IPV/Hib + HBV primed (N= 99 for ATP cohort for antibody persistence)
% = percentage of subjects with titres above the cut-off
95% CI = 95% Confidence Interval
*percentage of subjects with anti-diphtheria antibody titre ≥ 0.1 IU/ml by ELISA or ≥ 0.016 IU/ml on Vero-cell neutralization test

Post-Booster Immunogenicity:

One month after the booster dose, all but 2 subjects had anti-PRP antibody titres ≥ 0.15mcg/ml, and all but three had anti-PRP antibody titres ≥ 1 mcg/ml. Anti-PRP GMTs increased 95-fold from pre- to post- booster vaccination .

Name of Company: SmithKline Beecham Biologicals, Rixensart, Belgium **Name of Finished Product:** **Name of active substance:** DTPa-HBV-IPV/ Hib	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Table 2: Seroprotection rates and GMTs for anti-PRP antibodies one month after vaccination (ATP cohort for immunogenicity)

Timing	N	≥ 0.15 mcg/ml				≥ 1 mcg/ml				GMT		
		n	%	95% CI		N	%	95% CI		mcg/ml	95% CI	
Pre	391	323	82.6	78.5	86.2	114	29.2	24.7	33.9	0.513	0.451	0.582
Post	398	396	99.5	98.2	99.9	395	99.2	97.8	99.8	48.531	42.350	55.613

Pre = Pre-booster sample
Post = Post-vaccination blood sample obtained 1 month after the booster vaccine dose
N = number of subjects with available results
n / % = number / percentage of subjects with titres above the cut-off
95% CI = 95% Confidence Interval

One month after the booster vaccination, all subjects had seroprotective levels of anti-diphtheria and anti-tetanus antibodies (titres ≥ 0.1 IU/ml), all subjects had seroprotective levels of anti-polio 1, anti-polio 2 and anti-polio 3 antibodies (≥ 8 dilutions) and all but 5 subjects had seroprotective levels of anti-HBs antibodies (titres≥ 10 mIU/ml). All subjects were seropositive for anti-PT, anti-FHA and anti-PRN antibodies (titres ≥ 5 EL.U/ml), and at least 97.4% had a vaccine response for PT, FHA and PRN. All subjects seronegative for one of the pertussis antigens prior to booster vaccination, responded to the booster dose of that particular antigen.

Safety Results:

Redness at the injection site was the most frequently reported solicited local symptom during the four-day follow-up period. Fever was the most frequently reported solicited general symptom followed by irritability and drowsiness. Most local and general solicited symptoms were of grade 1 or 2 intensity.

Table 3: Incidence of total solicited symptoms and grade 3 solicited symptoms during the 4-day follow-up - pooled subgroups (ATP cohort for safety)

Symptom	Total			Grade 3		
	%	95% CI		%	95% CI	
Local (N=433)	**63.4**	**58.7**	**67.9**	**18.2**	**14.7**	**22.1**
Pain	39.0	34.4	43.7	6.4	4.3	9.1
Redness	53.1	48.3	57.8	10.0	7.4	13.2
Swelling	36.0	31.5	40.7	9.6	7.0	12.7
General (N=433)	**71.6**	**67.1**	**75.8**	**9.3**	**6.8**	**12.4**
Drowsiness	39.5	34.9	44.3	1.8	0.8	3.6
Fever	47.0	42.3	51.8	4.3	2.6	6.7
Irritability	44.5	39.8	49.3	3.0	1.6	5.0
Loss of Appetite	27.5	23.4	31.9	3.6	2.1	5.8

95% CI = 95% Confidence Interval
Fever = rectal temperatures ≥ 38° C or axillary temperature ≥ 37.5° C
Grade "3" pain = cried when limb was moved/spontaneously painful
Grade "3" redness\swelling > 20 mm in diameter
Grade "3" drowsiness = Drowsiness that prevents normal activity
Grade "3" fever = rectal temperature >39.5°C or axillary temperature >39.0°C
Grade "3" fussiness = Crying that could not be comforted / prevents normal activity
Grade "3" loss of appetite = Not eating at all

Name of Company: SmithKline Beecham Biologicals, Rixensart, Belgium **Name of Finished Product:** **Name of active substance:** DTPa-HBV-IPV/ Hib	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

One hundred and forty five subjects (108 in sub-group P1 and 37 in sub-group P2) reported at least one unsollcited symptom (as classified by WHO preferred terms) within 30 days after vaccination, of which 13 were assessed as probably or suspected to be related to vaccination.

Serious Adverse Events: Two serious adverse events were reported during the study course: Subjects n°277 was hospitalised 28 days after vaccination for febrile convulsions and suspected viral infection of unclear localisation. Subject n°498 was hospitalised 11 days after vaccination, for commotio cerebri. Both the SAEs resolved without sequelae and were determined by the investigator to be not related to vaccination.

Withdrawals due to adverse events: None

Conclusion(s):

- Similar pre-booster antibody persistence was observed for both primary vaccination regimens (i.e. similar pre-booster antibody levels following priming with DTPa-HBV-IPV/Hib and DTPa-IPV/Hib + HBV)
- One month after booster vaccination with DTPa-HBV-IPV/Hib, more than 99% of subjects had anti-PRP titres ≥1.0 mcg/ml, 100% had anti-diphtheria and anti-tetanus titres ≥0.1 IU/ml, 100% had anti-PT, anti-FHA, and anti-PRN titres ≥ 5 EL.U/ml, more than 98.7% had anti-HBs titres ≥10 mIU/ml, and 100% had anti-polio (types 1, 2 and 3) titres ≥8.
- The DTPa-HBV-IPV/Hib vaccine showed an acceptable safety and reactogenicity profile when give as a booster dose in the second year of life.

July 3, 2000

Document 1

Name nf Company: SmithKline Beecham Biologicals, Rixensart, Belgium Name of Finished Product: Name of active substance: DTPa-HepB-IPV	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	
Title of the study: A phase II, single-blinded, randomized comparative study of the safety and immunogenicity of a booster dose of SmithKline Beecham Biologicals' DTPa-HepB-IPV vaccine compared with Infanrix® when both vaccines are co-administered with OmniHIB® between 15 and 18 months of age following primary immunization at the age of 2, 4 and 6 months in the study DTPa-HepB-IPV-044 (CPMS N° 217744/044).		
Principal Investigator: s22 [redacted]		
Study Center(s):		
Primary Physicians Research 1580 McLaughlin Run Road Pittsburgh, PA 15241	Pediatric Alliance St. Clair 1580 McLaughlin Run Road, Suite 208 Pittsburgh, PA 15241	
Franklin Pediatrics 1141 Franklin Street Johnstown, PA 15905	Greenville Medical Center, Inc. 90 Shenango Street Greenville, PA 16125	
Greenville Pediatrics 103 Woodfield Drive Greenville, PA 16125	Pediatric Alliance Manor Oak 1910 Cochron Road Pittsburgh, PA 15220	
R/D Clinical Research, Inc. 135 Oyster Creek Drive, Suite W Lake Jackson, TX 77566	54 Flag Lake Plaza Lake Jackson, TX 77566	
Vanderbilt University Medical Center 1161 21st Avenue South Nashville, TN 37233-2195	Greenhills Pediatrics 2002 Richard Jones Road Nashville, TN 37215	
Hill Top Research, Inc. 6079 N. Fresno Street, Suite 101 Fresno, CA 93710	Center for Clinical Research-Austin 12221 N MoPac Expressway Austin, TX 78758	
Austin Diagnostic Clinic 12221 N. MoPac Expressway Austin, TX 78758	Austin Children's Clinic North 3508 Far West Blvd. Austin, TX 78731	
Austin Children's Clinic South 621 Radam Lane Austin, TX 78745		
Publication (reference): none as of this report.		
Study period: Date of first visit: 18 May 1999 Date of last visit: 30 November 1999	Clinical phase: II	

Document 1

Name of Company: SmithKline Beecham Biologicals, Rixensart, Belgium Name of Finished Product: Name of active substance: DTPa-HepB-IPV	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	

Objectives:

Primary:

- To evaluate the safety and reactogenicity of a booster dose of SB Biologicals' DTPa-HepB-IPV vaccine compared with *Infanrix* (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) when both vaccines are co-administered with *OmniHIB* (Haemophilus b Conjugate Vaccine) between 15 and 18 months of age.

Secondary:

- To demonstrate the immunogenicity of a booster dose of SB Biologicals' DTPa-HepB-IPV vaccine compared with *Infanrix* when both vaccines are co-administered with *OmniHIB* between 15 and 18 months of age.
- To assess the persistence just prior to booster vaccination of antibodies against all antigens given during the three-dose primary vaccination course of DTPa-HepB-IPV and *OmniHIB* administered as separate injections.

Methodology:

Study design: Randomized, single-blinded (subjects were not informed as to whether they received the DTPa vaccine or the DTPa-HepB-IPV vaccine), controlled, multiple center study. Balanced allocation in two groups (1:1) as follows:

Group 1: SB Biologicals' *Infanrix* + Aventis-Pasteur's *OmniHIB*

Group 2: SB Biologicals' DTPa-HepB-IPV + Aventis-Pasteur's *OmniHIB*.

Number of subjects:

Planned: 324 (162 in Group 1 and 162 in Group 2)

Enrolled: 196 (96 in Group 1 and 100 in Group 2)

Completed: 194 (95 in Group 1 and 99 in Group 2)

ATP cohort for safety: 193 (94 in Group 1 and 99 in Group 2)

ATP cohort for immunogenicity: 186 (90 in Group 1 and 96 in Group 2)

Diagnosis and criteria for inclusion:

Healthy infants at least 15 and not older than 18 months of age at the time of booster vaccination who had completed the primary series phase of SB protocol 217744/044 and had received three doses of DTPa-HepB-IPV vaccine. The parents/guardian provided written informed consent.

Duration of study participation: Approximately one month for each subject.

Test product, dose, mode of administration, batch number:

- SB Biologicals' liquid combined DTPa-HepB-IPV vaccine, containing per 0.5 mL dose to be administered IM: ≥ 2 U/mL (25 Lf) Diphtheria toxoid; ≥ 2 U/mL (10 Lf) Tetanus toxoid; 25 mcg PT; 25 mcg FHA; 8 mcg PRN; 10 mcg HBsAg (recombinant); 40D antigen units Poliovirus type 1 (Mahoney); 8D antigen units Poliovirus type 2 (MEF-1); 32D antigen units Poliovirus type 3 (Saukett); 2.5 mg 2-Phenoxyethanol; 150 mM Sodium chloride; 0.7 mg Aluminum as salts, ≤100 mcg Formalin; ≤25 mcg Neomycin sulfate; and ≤50 mcg Polysorbate, supplied as a turbid whitish suspension in 3 mL monodose glass vials. Three production lots of the DTPa-HBV-IPV vaccine were used as follows: Lots: D21728A2 (Expiry date: 10 June 2000), 21736A2 (Expiry date: 27 August 2000), and D21726A2 (Expiry date: 10 June 2000).
- AP's lyophilized *Haemophilus influenzae* type b vaccine (OmniHIB®), containing per 0.5 mL dose to be administered IM: 10 mcg PRP; 24 mcg Tetanus toxoid; 42.5 mg Sucrose; 0.6 mg TRIS, supplied in monodose vials containing a white freeze-dried pellet to be reconstituted before use with the saline diluent (0.4% NaCl) supplied in pre-filled syringes. Commercial lot: P0026 (*OmniHIB* vaccine); P0481 (saline diluent in pre-filled syringes). Expiry date for both the vaccine and the diluent: 05 March 2001.

Reference therapy, dose and mode of administration, batch number:

- SB Biologicals' liquid DTPa vaccine (Infanrix®), containing per 0.5 mL dose to be administered IM: ≥ 2 U/mL (25 Lf) Diphtheria toxoid; ≥ 2 U/mL (10 Lf) Tetanus toxoid; 25 mcg PT; 25 mcg FHA; 8 mcg PRN; 0.5 mg Aluminum as salts; 2.5 mg 2-phenoxyethanol; 150 mM Sodium chloride, supplied as a turbid white suspension in monodose vials. Commercial Lot: DTPa911A2. Expiry date: 11 June 2000.

Name of Company: SmithKline Beecham Biologicals, Rixensart, Belgium Name of Finished Product: Name of active substance: DTPa-HepB-IPV	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	

- AP's lyophilized *Haemophilus influenzae* type b vaccine (OmniHIB®), containing per 0.5 mL dose to be administered IM: 10 mcg PRP; 24 mcg Tetanus toxoid; 42.5 mg Sucrose; 0.6 mg TRIS, supplied in monodose vials containing a white freeze-dried pellet to be reconstituted before use with the saline diluent (0.4% NaCl) supplied in pre-filled syringes. Commercial lot: P0026 (*OmniHIB* vaccine). Commercial lot: P0481 (saline diluent in pre-filled syringes). Expiry date for both the vaccine and the diluent: 05 March 2000.

Criteria for evaluation:

Safety:

The primary endpoint was the occurrence of any grade 3 solicited symptoms within 8 days following booster vaccination. Solicited local symptoms (pain, redness, swelling at the injection site, and extensive swelling) and general symptoms (fever, irritability/fussiness, drowsiness and loss of appetite) were recorded during an 8-day follow-up period (day 0 – day 7) after vaccination. Unsolicited symptoms were to be recorded during a 30-day follow-up period after vaccination and serious adverse events (SAEs) during the entire study period.

Immunogenicity:

Measurement of anti-diphtheria, anti-tetanus, anti-PT, anti-FHA, anti-PRN, anti-HBs, and anti-poliovirus types 1, 2, and 3 antibody titers and anti-PRP concentrations, before and one month after the booster dose. Seroprotection status to PRP, HBs, diphtheria, tetanus and poliovirus 1, 2, and 3, seropositivity status and vaccine response to pertussis antigens were secondary endpoints. Vaccine response to the pertussis antigens was defined as the appearance of antibodies (titer ≥ 5 EI.U/mL) in initially seronegative subjects or a two-fold increase of pre-booster vaccination titers in initially seropositive subjects.

Statistical methods:

Descriptive analyses of the immunogenicity and reactogenicity data were performed as specified in the protocol. The primary analyses were performed on the ATP cohorts.

Safety:

The percentages of subjects with at least one adverse event (solicited and/or unsolicited, local or general), at least one local adverse event (solicited and/or unsolicited) and with at least one general adverse event (solicited and/or unsolicited) during the 8-day follow-up period after vaccination were tabulated for each group. Incidences were calculated for each solicited symptom with grade 3 intensity occurring during the 8-day follow-up period after vaccination and for solicited general symptoms with relationship to vaccination rated as "probable" or "suspected" (as per investigator assessment). Unsolicited symptoms occurring within 30 days after vaccination, classified by WHO preferred terms, were also tabulated overall and for those with relationship to vaccination rated as "probable" or "suspected". Serious adverse events and extensive swelling were described.

Immunogenicity:

Antibody persistence was evaluated for all vaccine antigens based on the calculation of pre-booster Geometric Mean Titers (GMT)/Geometric Mean Concentrations (GMC) with 95% CIs and seroprotection/seropositivity rates with 95% CIs according to the primary vaccine.

Immunogenicity after the booster vaccination was evaluated for all antigens in terms of GMTs and seroprotection/seropositivity rates with their 95% CIs and in addition for pertussis antigens in terms of vaccine response rates with exact 95% CIs.

As a complement to the descriptive analyses, two-sided exact 90% CIs for difference between booster groups (Group 1 minus Group 2) in seroprotection/vaccine response rates were computed for all antigens. For anti-PT, anti-FHA and anti-PRN, the two-sided 90% CIs for the GMT ratios between groups (Group 1 over Group 2) were computed using a one-way ANOVA model on the logarithm$_{10}$ transformation of the titers.

Reactogenicity Results

Table 1S presents the incidence and nature of grade 3 solicited symptoms reported during the solicited 8-day follow-up period following vaccination.

Table 1S: Incidence and nature of grade 3 solicited symptoms reported during the solicited 8-day follow-up period following vaccination -- ATP cohort for safety

Document 1

Name of Company: SmithKline Beecham Biologicals, Rixensart, Belgium Name of Finished Product: Name of active substance: DTPa-HepB-IPV	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	

	Group 1					Group 2				
	N	n	%	95 CI		N	n	%	95 CI	
				LL	UL				LL	UL
Any Symptoms	94	10	10.6	5.2	18.7	99	14	14.1	8.0	22.6
Any General Symptoms	94	4	4.3	1.2	10.5	99	7	7.1	2.9	14.0
Any Local* Symptoms	94	6	6.4	2.4	13.4	99	8	8.1	3.6	15.3

Group 1: Subjects receiving *Infanrix* (DTPa) + *OmniHIB*
Group 2: Subjects receiving DTPa-HepB-IPV + *OmniHIB*
N= number of subjects with at least one documented dose
n = number of subjects presenting at least one type of symptom
% = percentage of subject presenting at least one type of symptom
95% CI, LL, UL = 95% confidence interval, lower and upper limits
*Local : n= number of subjects presenting at least one local symptom whatever the number of injections. For local symptoms and multiple injections, a symptom was counted once even if reported on multiple sites

There was a slight increase in the observed percentage of subjects with at least one grade 3 solicited symptom in the candidate vaccine group (14.1%) compared to the control group (10.6%) but there was no evidence that this increase was attributed to a true increase rather than to natural variability as shown by the 95% CI largely overlapping the observed percentage of the other group.

Table 2S presents the incidence of any intensity of solicited local symptoms following the booster vaccination.

Table 2S: Incidence of any intensity of solicited local symptoms during the 8-day follow-up period following vaccination – ATP cohort for safety

		Group 1 N = 94				Group 2 N = 99			
	Intensity	n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
Pain	Any	38	40.4	30.4	51.0	39	39.4	29.7	49.7
	grade 3	1	1.1	0.0	5.8	1	1.0	0.0	5.5
Redness	Any	44	46.8	36.4	57.4	50	50.5	40.3	60.7
	grade 3	4	4.3	1.2	10.5	5	5.1	1.7	11.4
Swelling	Any	32	34.0	24.6	44.5	28	28.3	19.7	38.2
	grade 3	2	2.1	0.3	7.5	5	5.1	1.7	11.4

Group 1: Subjects receiving *Infanrix* (DTPa) + *OmniHIB*
Group 2: Subjects receiving DTPa-HepB-IPV + *OmniHIB*
Any = local symptoms reported for any vaccination site during the 8 day follow-up period
* = DTPa for Group 1 and DTPa-HepB-IPV for Group 2
N = number of subjects with at least one symptom sheet completed
n = number of subjects reporting a specified symptom
% = percentage of subjects reporting a specified symptom
95% CI, LL, UL = 95% confidence interval, lower and upper limits

Table 3S presents data on the incidence and intensity of solicited general symptoms following the booster vaccination.

Table 3S: Incidence and intensity of solicited general symptoms during the 8-day follow-up period – ATP cohort for safety

Name of Company: SmithKline Beecham Biologicals, Rixensart, Belgium Name of Finished Product: Name of active substance: DTPa-HepB-IPV	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	

		Group 1 N = 94				Group 2 N = 98			
		n	%	95% CI		n	%	95% CI	
	Intensity			LL	UL			LL	UL
Drowsiness	Any	34	36.2	26.5	46.7	38	38.8	29.1	49.2
	grade 3	2	2.1	0.3	7.5	0	0.0	0.0	3.7
Fever	Any	31	33.0	23.6	43.4	31	31.6	22.6	41.8
	grade 3	0	0.0	0.0	3.8	3	3.1	0.6	8.7
Irritability	Any	52	55.3	44.7	65.6	63	64.3	54.0	73.7
	grade 3	2	2.1	0.3	7.5	2	2.0	0.2	7.2
Loss of Appetite	Any	34	36.2	26.5	46.7	42	42.9	32.9	53.3
	grade 3	2	2.1	0.3	7.5	0	0.0	0.0	3.7

Group 1: Subjects receiving *Infanrix* (DTPa) + *OmniHIB*
Group 2: Subjects receiving DTPa-HepB-IPV + *OmniHIB*
N = number of subjects with at least one symptom sheet completed
n = number of subjects reporting a specified grade 3 symptom
% = percentage of subjects reporting a specified symptom
95% CI, LL, UL = 95% confidence interval, lower and upper limits
Onset 2 days = onset on day 0, 1 or 2 following vaccination
Total = onset on day 0-7 following vaccination

The low occurrence of grade 3 symptoms support the acceptability of DTPs-HepB-IPV as a booster dose.

No withdrawals were due to an adverse event. No serious adverse events were reported. Two extensive swellings were reported (both in Group 2).

Immunogenicity Results

Table 4S presents the post-booster seroprotection and vaccine response rates for the ATP cohort for immunogenicity.

Table 4S: Seroprotection/vaccine response rates following the booster dose - ATP cohort for Immunogenicity

	Group 1		Group 2	
Endpoints	N	%	N	%
anti-D ≥0.1 IU/mL	90	100	96	100
anti-T ≥0.1 IU/mL	90	100	96	100
anti- PT vaccine response	90	98.9	92	98.9
anti- FHA vaccine response	90	97.8	92	98.9
anti- PRN vaccine response	90	98.9	92	100
anti-PRP ≥ 0.15 mcg/mL	90	100	96	100
anti-PRP ≥ 1 mcg/mL	90	100	96	99.0

Document 1

Name of Company: SmithKline Beecham Biologicals, Rixensart, Belgium Name of Finished Product: Name of active substance: DTPa-HepB-IPV	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	

Group 1: Subjects receiving *Infanrix* (DTPa) + *OmniHIB*
Group 2: Subjects receiving DTPa-HepB-IPV + *OmniHIB*
% = percentage of subjects in a given category
N = number of subjects with available results

Table 5S presents the seroprotection/seropositivity rates and geometric mean titers/concentrations pre- and post-booster dose for the ATP cohort for immunogenicity.

Table 5S: Seroprotection/seropositivity rates and geometric mean titers/concentrations pre- and post-booster dose – ATP cohort for immunogenicity

		Group 1			Group 2		
Endpoints		**N**	**%**	**GMT**	**N**	**%**	**GMT**
anti-D ≥0.1 IU/mL	Pre B	90	36.7	0.081	92	31.5	0.080
	Post B	90	100.0	2.525	96	100.0	2.613
anti-T ≥0.1 IU/mL	Pre B	90	96.7	0.509	92	96.7	0.403
	Post B	90	100.0	10.859	96	100.0	9.107
anti-PT ≥5 EL.U/mL	Pre B	90	67.8	7.8	92	66.3	7.1
	Post B	90	100.0	116.7	96	100.0	146.6
anti-FHA ≥5 EL.U/mL	Pre B	90	94.4	21.6	92	98.9	21.5
	Post B	90	100.0	270.1	96	100.0	335.7
anti-PRN ≥5 EL.U/mL	Pre B	90	86.7	12.8	92	77.2	11.7
	Post B	90	100.0	294.7	96	100.0	320.7
anti-HBs ≥10 mIU/mL	Pre B	90	96.7	239.0	92	90.2	124.2
	Post B	90	97.8	224.9	96	99.0	6783.7
anti-poliovirus 1 ≥8	Pre B	90	93.3	78.5	91	96.7	68.0
	Post B	90	94.4	49.7	96	100.0	1208.9
anti-polivirus 2 ≥8	Pre B	90	95.6	81.2	91	98.9	91.5
	Post B	90	93.3	67.5	96	100.0	1766.2
anti-poliovirus 3 ≥8	Pre B	90	97.8	188.1	91	97.8	177.5
	Post B	90	97.8	155.3	96	100.0	3215.9
anti-PRP ≥0.15 mcg/mL	Pre B	90	94.4	0.708	92	94.6	0.698
	Post B	90	100.0	35.319	96	100.0	40.356
anti-PRP ≥1 mcg/mL	Pre B	90	34.4		92	35.9	
	Post B	90	100.0		96	99.0	

Name of Company: SmithKline Beecham Biologicals, Rixensart, Belgium Name of Finished Product: Name of active substance: DTPa-HepB-IPV	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	

Group 1: Subjects receiving *Infanrix* (DTPa) + *OmniHIB*
Group 2: Subjects receiving DTPa-HepB-IPV + *OmniHIB*
Pre B = Pre-booster
Post B = Post-booster
N = number of subjects with available results
%=percentage of subjects with titers/concentrations within the specified range

There was a substantial increase from pre- to post-booster for all antigens except for polio and HBs in Group 1 in which the booster vaccination did not include these antigens. In terms of seroprotection rates, for most of the antigens (T, HBs, polio and PRP – all above 90%) the rate before vaccination was too high to allow the post-vaccination measurement to reflect a booster effect and thereby to discriminate between the booster vaccines.

Conclusions:

- The combination candidate DTPa-HepB-IPV vaccine and DTPa (Infanrix) vaccine were safe, well-tolerated, and immunogenic when administered as a booster dose and coadministered with Hib vaccine in children 15 to 18 months of age.
- There was a low occurrence of grade 3 local and general solicited symptoms within 8 days following the booster vaccination in both groups.
- The observed percentage of children for whom solicited local and general symptoms were reported within 8 days following booster vaccination or for whom unsolicited symptoms were reported within 30 days following booster vaccination was similar in each of the vaccine groups. There were no serious adverse events reported during the course of the trial.
- There were no differences between the groups of children boosted with DTPa-HepB-IPV and Hib vaccines or those boosted with DTPa and Hib vaccines in the rates of seroprotection for diphtheria, tetanus or Hib or in vaccine response rates to the pertussis antigens (PT, FHA and PRN). Pre booster antibody levels indicate good antibody persistence in the cohort participating in the current booster study.

Date of report: 12 January 20010

Name of Company: SmithKline Beecham Biologicals, Rixensart, Belgium **Name of Finished Product:** - **Name of active substance:** DTPa-HBV-IPV vaccine	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Title of the study: Open, multicentre, phase III clinical study to assess the immunogenicity and reactogenicity of SB Biologicals' DTPa-HBV-IPV and Hib conjugate vaccines when mixed extemporaneously and administered in a single injection as a booster dose to 12 to 15 months old healthy children, previously vaccinated at the age of 6, 10 and 14 weeks in primary vaccination study DTPa-HBV-IPV-040 (217744/040), with three doses of the same vaccines either or not following a single dose of SB Biologicals' HBV vaccine (*Engerix™-B*) at birth.

Principal Investigators: s22 [redacted]

Study Centre(s): 8 study sites in the Philippines

Publication (reference): Not published as of August 22, 2000

Study period: Date of first visit: November 5, 1999 Date of last visit: February 29, 2000	**Clinical phase:** III

Objectives:

Primary:

To assess the reactogenicity of the study vaccines in terms of grade 3 local and general solicited symptoms.

Secondary:

- To assess the reactogenicity of the study vaccines in terms of solicited symptoms, unsolicited symptoms and serious adverse events.
- To assess the immune response to the booster dose.
- To assess the persistence of antibodies to all the antigens contained in SB Biologicals' DTPa-HBV-IPV/Hib vaccine prior to booster vaccination.

Methodology:

This was an open, multicenter, booster study with two parallel groups designed as an extension of the primary vaccination study. In this booster study, both groups received a DTPa-HBV-IPV/Hib booster at 12 to 15 months of age following primary vaccination with DTPa-HBV-IPV/Hib in study DTPa-HBV-IPV-040. Group 2 received a dose of HBV at birth and group 1 did not.

Two blood samples were taken, one immediately before the booster, and the other one month after booster vaccination.

Number of subjects:

Enrolled in primary study and planned for booster study: 320
Enrolled in booster study ITT cohort: 237 (113 in group 1 and 124 in group 2)
Completed booster study: 227 (107 in group 1 and 120 in group 2)
ATP cohort for safety: 228 (108 in group 1 and 120 in group 2)
ATP cohort for immunogenicity: 212 (101 in group 1 and 111 in group 2)

Diagnosis and criteria for inclusion:

Healthy infants, 12-15 months of age previously primed at the age of 6, 10 and 14 weeks, with three doses of DTPa-HBV-IPV/Hib in Study 217744/040 (DTPa-HBV-IPV-040). Subject's parent(s)/guardian(s) must have provided written, informed consent. The children must have been free of obvious health problems as established by medical history and clinical examination before entering the study.

Name of Company: SmithKline Beecham Biologicals, Rixensart, Belgium **Name of Finished Product: -** **Name of active substance:** DTPa-HBV-IPV vaccine	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Test product, dose, mode of administration, lot No.:

Vaccination schedule/site: One booster vaccination given in the second year of life (12-15 months of age).

Vaccines: SB's combined diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated polio (DTPa-HBV-IPV) vaccine per 0.5 ml: diphtheria toxoid ≥30 IU (25 Lf), tetanus toxoid ≥40 IU (10 Lf), pertussis toxoid (PT) 25 mcg, filamentous haemagglutinin (FHA) 25 mcg, pertactin (PRN), 8 mcg, hepatitis B surface antigen (HBsAg) 10 mcg, polio virus type 1 (Mahoney strain) 40D antigen units, polio virus type 2 (MEF-1 strain) 8D antigen units, polio virus type 3 (Saukett strain) 32D antigen units, aluminium as salts 0.7 mg and phenoxyethanol <2.5 mg. Lot number D21799B2 was used.
SB's *Haemophilus influenzae* type b (Hib) conjugate lyophilized vaccine, containing per dose of 0.5 ml (after reconstitution): Polyribosyl Ribitol Phosphate (PRP) 10 mcg, Tetanus toxoid 20-40 mcg, Lactose 10 mg and aluminium as salts 0.12 mg.
Lot number DHib200A41 was used.

Site: Both groups received SB's DTPa-HBV-IPV/Hib intramuscular injection in the left anterolateral thigh.

Duration of treatment: Approximately one month for all subjects

Reference therapy: Not applicable.

Criteria for evaluation:

Safety:

The primary endpoint was the occurrence of grade 3 solicited symptoms within 8 days following booster vaccination. Solicited local symptoms (pain, redness and swelling at the injection site) and general symptoms (fever, irritability, loss of appetite, restlessness and sleeping more than usual), were recorded during an 8-day follow-up period after vaccination. Recording of unsolicited symptoms during a 30-day follow-up period after vaccination and of serious adverse events (SAE) during the entire study period.

Immunogenicity:

Measurement of anti-PRP, anti-HBs, anti-diphtheria, anti-tetanus, anti-PT, anti-FHA and anti-PRN and anti-polio types 1, 2, 3 antibody titres before and one month after the booster dose. Seroprotection rates to PRP, HBs, diphtheria, tetanus and polio 1, 2, 3 and seropositivity, and vaccine response rates to pertussis antigens (PT, FHA, PRN) were measured. Vaccine response to the pertussis antigens was defined as the appearance of antibodies (titre ≥ 5 ELU/ml) in initially seronegative subjects or a two-fold increase of pre-booster vaccination titres in initially seropositive subjects. GMTs were computed for all antigens before and after the booster dose.

Statistical methods: Analyses of the immunogenicity and reactogenicity data were descriptive only as specified in the protocol. The primary analyses were performed on the ATP cohort. Analyses were performed as planned in the protocol.

Safety:

The percentages of subjects with at least one adverse event (solicited and/or unsolicited, local or general), at least one local adverse event (solicited and/or unsolicited) and with at least one general adverse event (solicited and/or unsolicited), during the 8-day follow-up period after vaccination, were tabulated. The incidence of each solicited symptom occurring during the 8-day follow-up period after vaccination was investigated overall, for solicited symptoms with grade 3 intensity, and for solicited general symptoms with relationship to vaccination rated as "probable" or "suspected" (as per investigator assessment).

Unsolicited symptoms occurring within 30 days after vaccination, classified by WHO preferred terms, were also tabulated overall and for those with relationship to vaccination rated as "probable" or "suspected". Serious adverse events were described.

Name of Company: SmithKline Beecham Biologicals, Rixensart, Belgium **Name of Finished Product:** - **Name of active substance:** DTPa-HBV-IPV vaccine	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Immunogenicity:

Antibody persistence was evaluated for all vaccine antigens based on the calculation of GMTs with 95% CI's, and seropositivity/seroprotection rates with 95% CI's on serology results obtained approximately one month after the primary vaccination and immediately before the booster dose.

Immunogenicity after the booster vaccination was evaluated for all antigens in terms of GMTs and seroprotection/seropositivity rates with their 95% CI's and for pertussis antigens in terms of vaccine response rates with exact 95% CI's.

SUMMARY-CONCLUSIONS:

Safety and reactogenicity of booster dose

The incidence of any symptom and of all local solicited symptoms, fever and irritability reported during the 8-day follow-up period after booster vaccination is presented in Table 1.

Table 1: Incidence of local solicited symptoms, fever and irritability* reported during the 8-day follow-up period after booster vaccination (ATP cohort for safety)

		Group 1, N = 108				Group 2, N = 120			
Symptoms		n	%	95% CI		n	%	95% CI	
ANY SYMPTOM	Total	87	80.6	71.8	87.5	94	78.3	69.9	85.3
	Grade 3	19	17.6	10.9	26.1	22	18.3	11.9	26.4
ANY LOCAL	Total	73	67.6	57.9	76.3	75	62.5	53.2	71.2
	Grade 3	16	14.8	8.7	22.9	15	12.5	7.2	19.8
Pain	Total	54	50.0	40.2	59.8	55	45.8	36.7	55.2
	Grade 3	6	5.6	2.1	11.7	6	5.0	1.9	10.6
Redness	Total	54	50.0	40.2	59.8	60	50.0	40.7	59.3
	> 20 mm	7	6.5	2.6	12.9	9	7.5	3.5	13.8
Swelling	Total	43	39.8	30.5	49.7	46	38.3	29.6	47.6
	> 20 mm	11	10.2	5.2	17.5	9	7.5	3.5	13.8
ANY GENERAL	Total	74	68.5	58.9	77.1	75	62.5	53.2	71.2
	Grade 3	5	4.6	1.5	10.5	10	8.3	4.1	14.8
Fever	≥ 37.5°C	52	48.1	38.4	58.0	50	41.7	32.7	51.0
	> 39.0°C	3	2.8	0.6	7.9	6	5.0	1.9	10.6
	PB/SU	45	41.7	32.3	51.5	46	38.3	29.6	47.6
Irritability	Total	46	42.6	33.1	57.5	49	40.8	32.0	50.2
	Grade 3	1	0.9	0.0	5.1	4	3.3	0.9	8.3
	PB/SU	41	38.0	28.8	47.8	44	36.7	78.1	45.9

Group 1: DTPa-HBV-IPV/Hib primed and boosted; Group 2: HBV at birth, DTPa-HBV-IPV/Hib primed and boosted
N: number of subjects with at least one symptom sheet completed
n/% : number/percentage of subjects reporting a specific symptom; 95% CI: 95% confidence interval
grade 3 pain = cried when the limb was moved/spontaneously painful (prevented normal everyday activity)
grade 3 irritability = crying/irritability could not be comforted; fever = axillary temperature
PB/SU = There probably was a direct cause and effect relationship between the adverse event and the study vaccine or a direct cause and effect relationship between the drug and the adverse experience was not demonstrated but there was a reasonable possibility that the experience was caused by the vaccine.
*Only the most frequently reported solicited general symptoms (fever and irritability) are presented in the synopsis. Other solicited general symptoms included loss of appetite, restlessness and sleeping more than usual.

- Overall incidence of symptoms (any or grade 3) was similar between groups (any: 80.6% and 78.3%; grade 3: 17.6% and 18.3% in groups 1 and 2 respectively).
- Pain and redness were the most frequently reported solicited local symptoms in both groups.
- The incidence of grade 3 local solicited symptoms was similar between groups.
- The incidence of solicited general symptoms were similar between groups.
- Fever was the most frequently reported general symptom in both groups.

Name of Company: SmithKline Beecham Biologicals, Rixensart, Belgium **Name of Finished Product: -** **Name of active substance:** DTPa-HBV-IPV vaccine	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

- Fever grade 3 was reported after 2.8% and 5% of the doses in groups 1 and 2 respectively.
- Of the 228 subjects with documented doses, 15 in group 1 and 21 in group 2 reported at least one unsolicited symptom during the 30 days following the booster dose.
- Three subjects (1 in group 1 and 2 in group 2) reported a total of eight unsolicited symptoms considered by the investigator to be probably related or was suspected of being related to vaccination.
- Four serious adverse events (SAEs) were reported during the study period (subject numbers 164, 169, 199 and 224 in group 2). Two of these SAEs were assessed by the investigator as probably related to vaccination (subj. no. 169: gastroenteritis and dehydration; sub. no. 224: vomiting and dehydration).
- None of the subjects dropped out because of an SAE.

Immunogenicity

Pre-booster antibody persistence persistence at 12-15 months of age (8.5 to 11.5 months after the primary vaccination:

Antibody persistence in terms of seroprotection/seropositivity rates and GMTs was similar between groups (except for anti-HBs where rates were higher in group 2), confirming the necessity of a dose of HBV at birth when priming according to age 6, 10, 14 weeks schedule (see Table 2).

Table 2: Percentage of seropositive/seroprotected subjects and GMTs prior to booster vaccination (ATP cohort for antibody persistence)

Antibody	Cut-off	Group	%	95% CI		GMT	95% CI	
Anti-PRP	≥ 0.15 mcg/ml	1	87.9	80.1	93.4	0.794	0.563	1.120
		2	85.8	78.3	91.5	0.824	0.608	1.116
Anti-Diphtheria*	≥ 0.1 IU/ml	1	91.7	84.4	95.9	0.076	0.066	0.088
	≥ 0.016 IU/ml	2	89.8	84.3	95.3	0.067	0.060	0.074
Anti-Tetanus	≥ 0.1 IU/ml	1	86.0	77.9	91.9	0.253	0.212	0.301
		2	79.8	71.5	86.6	0.215	0.181	0.256
Anti-PT	≥ 5 EL.U/ml	1	67.6	57.8	76.4	7.2	6.0	8.7
		2	63.6	54.2	72.2	6.0	5.2	7.1
Anti-FHA	≥ 5 EL.U/ml	1	95.4	89.5	98.5	20.8	17.0	25.4
		2	96.6	91.5	99.1	18.6	15.5	22.2
Anti-PRN	≥ 5 EL.U/ml	1	64.8	55.0	73.8	7.6	6.1	9.3
		2	72.3	63.3	80.1	9.5	7.7	11.7
Anti-HBs	≥ 10 mIU/ml	1	61.1	51.3	70.3	23.7	17.7	31.8
		2	89.9	83.0	94.7	109.1	82.1	145.0
Anti-Polio 1	≥ 8	1	89.7	81.3	95.2	51.2	37.4	70.2
		2	94.1	87.5	97.8	48.9	38.2	62.6
Anti-Polio 2	≥ 8	1	92.0	84.3	96.7	57.1	42.3	77.0
		2	86.0	77.6	92.1	44.6	33.0	60.1
Anti-Polio 3	≥ 8	1	94.3	87.1	98.1	73.4	53.1	101.5
		2	97.0	91.5	99.4	85.4	66.0	110.5

Group 1: DTPa-HBV-IPV/Hib primed and boosted. Group 2: HBV at birth, DTPa-HBV-IPV/Hib primed and boosted
*Either anti-diphtheria antibody titre ≥0.1 IU/ml by ELISA or detectable neutralising anti-diphtheria antibodies in an *in vitro* neutralisation test on VERO cells (≥0.016 IU/ml)

Name of Company: SmithKline Beecham Biologicals, Rixensart, Belgium **Name of Finished Product: -** **Name of active substance:** DTPa-HBV-IPV vaccine	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Post booster immunogenicity one month after booster vaccination:

- In both groups there was a similar and substantial increase in GMTs for all antibodies from pre- to post-booster.
- All subjects in both groups had anti-PRP titres ≥ 0.15 mcg/ml and 99% had anti-PRP titres ≥ 1.0 mcg/ml
- 90% and 99.1% of the subjects in groups 1 and 2, respectively, had anti-HBs titres ≥10 mIU/ml
- At least 99% of the subjects in both groups had anti-diphtheria and anti-tetanus antibody titres ≥ 0.1 IU/ml
- All of the subjects in both groups had anti-PT, anti-FHA and anti-PRN antibody titres ≥ 5 El.U/ml with at least 97.9% of the subjects in both groups having a vaccine response to each of the pertussis antigens

Conclusions:

- The incidences of solicited local and general symptoms were similar between groups.
- SB's DTPa-HBV-IPV vaccine appeared to be safe and well-tolerated as a booster dose following a three dose primary vaccination schedule, either with or without an additional dose of hepatitis B (HB) vaccine given at birth.
- Pre-booster antibody titres were similar between groups except for anti-HBs antibody titres, which were higher in the group that received an extra dose of HBV at birth.
- In terms of immunogenicity, no substantial differences were observed between the two groups except that anti-HBs antibody titres were higher in the group that received an extra dose of HB vaccine at birth.

Study report date: Aug 22, 2000

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium Name of Finished Product: Infanrix™ hexa, Priorix™ and Varilrix™ Name of active substance: Diphtheria and tetanus toxoids, PT, PRN, FHA, HBsAg, poliovirus types 1, 2, 3, PRP Live attenuated measles, mumps, rubella vaccine Live attenuated varicella vaccine	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

Title of the study: 217744/065 (DTPa-HBV-IPV-065)

Open, randomized, multicenter, phase III clinical trial to assess the reactogenicity and immunogenicity of a booster dose of GlaxoSmithKline (GSK) Biologicals' DTPa-HBV-IPV/Hib vaccine, co-administered during the same visit with GSK Biologicals' MMR or Varicella vaccine, in children in their second year of life, previously vaccinated in the DTPa-HBV-IPV-039, -041, -043 or-057 primary vaccination studies.

Principal Investigator: S22 [redacted]

Study Center: UniKlinik Mainz, Langenbeck Street 1, 55101, Mainz.

Publication (reference): Not published as of 27 August 2004

Study period: Date of first visit: 7 December 1999 Date of last visit: 22 October 2000	**Clinical phase:** III

Objectives:

Primary:

- To assess the reactogenicity of the study vaccines in terms of grade "3" local or general, solicited or unsolicited symptoms occurring within 4 days after vaccination.

Secondary:

- To assess the safety and reactogenicity of the study vaccines in terms of solicited symptoms, unsolicited symptoms and serious adverse events.
- To assess the immune response to the study vaccines.
- To assess the persistence of antibodies to all the antigens contained in GSK Biologicals' combined DTPa-HBV-IPV/Hib vaccine prior to booster vaccination.

Methodology:

Study design: An open, multicentric (24 centers) study with 3 parallel groups:

- Group 1 received DTPa-HBV-IPV mixed with Hib vaccine (DTPa-HBV-IPV/Hib) + measles, mumps, rubella vaccine (Priorix™)
- Group 2 received DTPa-HBV-IPV/Hib vaccine+ varicella vaccine (Varilrix™)
- Group 3 received DTPa-HBV-IPV/Hib vaccine as a control

A blood sample was taken at Visits 1 (Day 0) and 2 (Day 42 – 56)

Number of subjects:

Planned: 240 (80 per group) Enrolled: 175 (Group 1: 59; Group 2: 57; Group 3: 59)
Completed: 175 (Group 1: 59; Group 2: 57; Group 3: 59)
Analysed for safety according-to-protocol (ATP) : 173 (Group 1: 58; Group 2: 56; Group 3: 59)
Analysed for immunogenicity ATP: 157 (Group 1: 55; Group 2: 50; Group 3: 52)

Diagnosis and criteria for inclusion:

A healthy male or female subject ≥ 12 and < 24 months of age at the time of first vaccination and for whom written informed consent was received from the parent/guardian. Having received a complete primary vaccination course in studies DTPa-HBV-IPV-039, 041, 043 or 057 (217744/039, 041, 043 or 057) in Germany, must not have had previous or intercurrent diphtheria, tetanus, pertussis, polio, hepatitis B, Hib, booster vaccination(s) or disease nor

Document 1

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium Name of Finished Product: Infanrix™ hexa, Priorix™ and Varilrix™ Name of active substance: Diphtheria and tetanus toxoids, PT, PRN, FHA, HBsAg, poliovirus types 1, 2, 3, PRP Live attenuated measles, mumps, rubella vaccine Live attenuated varicella vaccine	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

previous or intercurrent measles, mumps, rubella and/or varicella vaccination(s) or disease.

Test product, dose, mode of administration, lot No.:

Vaccination schedule/site: Group 1 received a single dose of DTPa-HBV-IPV/Hib vaccine intramuscularly (IM) in the left thigh + Priorix™ subcutaneously (SC) in the right deltoid region at ≥ 12 months of age. Group 2 received a single dose of DTPa-HBV-IPV/Hib vaccine IM in the left thigh + Varilrix™ SC in the right deltoid region at ≥ 12 months of age.

Vaccine/composition/dose/lot number: After reconstitution of the lyophilized Hib component (Lot No.: Hib402A47/M, DHib200A41) using the liquid DTPa-HBV-IPV (Lot No.: D21799B2), one dose (0.5 ml) of GSK Biologicals' DTPa-HBV-IPV/Hib vaccine contained: ≥ 30 IU of diphtheria toxoid, ≥ 40 IU of tetanus toxoid, three acellular pertussis antigens: 25 µg of pertussis toxoid (PT), 25 µg of filamentous haemagglutinin (FHA) and 8 µg of pertactin (PRN), 10 µg of recombinant hepatitis B surface antigen (HBsAg), 40 D antigen units of poliovirus type 1, 8 D antigen units of poliovirus type 2, 32 D antigen units of poliovirus type 3, 10 µg of polyribosyl-ribitol phosphate (PRP) conjugated to 20-40 µg of tetanus toxoid, 0.82 mg of aluminium as salts, 12.6 mg of lactose, ≤ 2.5 mg of 2-phenoxyethanol, 150 mM of Sodium chloride, ! 100 µg of formalin, ! 25 µg of neomycin sulphate and ! 50 µg of Polysorbate.

GSK Biologicals' combined Measles Mumps Rubella vaccine (Priorix™) containing per 0.5 ml dose (after reconstitution with diluent lot no. 99B10/278, 99G07/300): ≥ $10^{3.0}$ $TCID_{50}$ Schwarz measles strain, ≥ $10^{3.7}$ $TCID_{50}$ RIT 4385 mumps strain, ≥ $10^{3.0}$ $TCID_{50}$ RA 27/3 rubella strain, 32 mg Lactose, 8 mg Mannitol, 9 mg Sorbitol, 9 mg Amino acids for injection, 1 mg Human serum albumin, 25 µg Neomycin sulphate, Lot no.: MJR212A41, MJR173A44.

GSK Biologicals' varicella vaccine (Varilrix™) containing per 0.5 ml dose (after reconstitution with diluent lot no. 98A96/249,98J06/267): > $10^{3.3}$ pfu Oka attenuated varicella strain, 40 mg Lactose, max. 10 mg Mannitol, 7-11 mg Sorbitol, 10-11.3 mg Amino acids for injection, 1 mg Human albumin, max. 25 µg Neomycin sulphate, Lot no.: VA212A44B, VA207A44B.

Reference therapy, dose and mode of administration, batch number:

Vaccination schedule/site: Group 3 received DTPa-HBV-IPV/Hib vaccine IM in the left thigh at ≥ 12 months of age. The DTPa-HBV-IPV and Hib components used were of the same composition and lot no. as mentioned above.

Duration of treatment: Approximately one month per subject.

Criteria for evaluation:

Primary endpoint

- Occurrence of any grade "3" symptom within 4 days after vaccination.

Secondary endpoints

- Occurrence and intensity of solicited local symptoms within 4 days after vaccination.
- Occurrence, intensity and relationship to vaccination of solicited general symptoms within 4 days after vaccination.
- Occurrence, intensity and relationship to vaccination of specific solicited general symptoms (fever, rash/exanthema, parotid/salivary gland swelling, suspected signs of meningism) after MMR vaccination (Day 0 – 42).
- Occurrence, intensity and relationship to vaccination of specific solicited general symptoms (fever, rash/exanthema) after Varicella vaccination (Day 0 – 42).
- Occurrence, intensity and relationship to vaccination of unsolicited symptoms within 42 days after vaccination.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium Name of Finished Product: Infanrix™ hexa, Priorix™ and Varilrix™ Name of active substance: Diphtheria and tetanus toxoids, PT, PRN, FHA, HBsAg, poliovirus types 1, 2, 3, PRP Live attenuated measles, mumps, rubella vaccine Live attenuated varicella vaccine	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

- Occurrence, intensity and relationship to vaccination of serious AEs throughout the study, up to and including 42 days post-vaccination.

Pre-vaccination immunological status:

- Anti-diphtheria and anti-tetanus toxoid, anti-PT, anti-PRN, anti-FHA, anti-PRP, anti-HBs and anti-poliovirus types 1, 2 and 3 antibody titres/concentrations.
- Seroprotection status: anti-PRP antibody concentration ≥ 0.15 µg/ml and ≥ 1.0 µg/ml, anti-diphtheria toxoid antibody concentration ≥ 0.1 IU/ml, anti-tetanus toxoid antibody concentration ≥ 0.1 IU/ml, anti-poliovirus type 1 antibody titre ≥ 8, anti-poliovirus type 2 antibody titre ≥ 8, anti-poliovirus type 3 antibody titre ≥ 8, anti-HBsAg antibody concentration ≥ 10 mIU/ml
- Seropositivity status: anti-PT antibody concentration ≥ 5 EL.U/ml, anti-PRN antibody concentration ≥ 5 EL.U/ml, anti-FHA antibody concentration ≥ 5 EL.U/ml.

In Group 1:

- Anti-measles, anti-mumps and anti-rubella antibody concentration
- Seroprotection status: anti-measles antibody concentration ≥ 150 mIU/ml, anti-rubella antibody concentration ≥ 4 IU/ml.
- Seropositivity status: anti-mumps antibody concentration ≥ 231 U/ml.

In Group 2:

- Anti-varicella antibody titre
- Seropositivity status: anti-varicella antibody titre ≥ 1/32.

Immunogenicity 42 to 56 days after vaccination:

- Anti-diphtheria and anti-tetanus toxoids, anti-PT, anti-PRN, anti-FHA, anti-PRP, anti-poliovirus types 1, 2 and 3, and anti-HBs antibody titres/concentration in all subjects
- Anti-measles, anti-mumps and anti-rubella antibody titres in subjects in Group 1 and anti-varicella antibody concentration in subjects in Group 2
- Seroprotection status: anti-PRP antibody concentration ≥ 0.15 µg/ml and ≥ 1.0 µg/ml , anti-diphtheria toxoid antibody concentration ≥ 0.1 IU/ml, anti-tetanus toxoid antibody concentration ≥ 0.1 IU/ml, anti-poliovirus type 1 antibody titre ≥ 8, anti-poliovirus type 2 antibody titre ≥ 8, anti-poliovirus type 3 antibody titre ≥ 8, anti-HBsAg antibody concentration ≥ 10 mIU/ml, anti-measles antibody concentration ≥ 150 mIU/ml (Group 1), anti-rubella antibody concentration ≥ 4 IU/ml (Group 1)
- Seropositivity status: anti-PT antibody concentration ≥ 5 EL.U/ml, anti-PRN antibody concentration ≥ 5 EL.U/ml, anti-FHA antibody concentration ≥ 5 EL.U/ml, anti-mumps antibody concentration ≥ 231 U/ml (Group 1), anti-varicella antibody titre ≥ 1/32 (Group 2).
- Booster vaccination response to PT, PRN and FHA 42 – 56 days after the booster dose, defined as appearance of antibodies in subjects who were initially (before booster vaccination) seronegative or at least a two-fold increase in antibody concentration between pre-booster and post-booster vaccination in subjects who were initially seropositive.

Note: The cut off of 1:4 was used for analysis of seropositivity for the varicella response as done in previous studies conducted with GSK Biologicals' MMR vaccine and varicella vaccine.

Statistical methods:

Safety:

The analysis was performed on the ATP cohort. The percentage of subjects reporting any grade "3" symptom, at least one grade "3" local/general symptom was tabulated per group with exact 95% confidence interval (CI). For each group, the percentage of subjects reporting each solicited local symptom (overall and grade "3") each solicited general symptom (overall, with

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium Name of Finished Product: Infanrix™ hexa, Priorix™ and Varilrix™ Name of active substance: Diphtheria and tetanus toxoids, PT, PRN, FHA, HBsAg, poliovirus types 1, 2, 3, PRP Live attenuated measles, mumps, rubella vaccine Live attenuated varicella vaccine	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

grade "3" intensity , with a 'suspected' or 'probable' ('PB'/'SU') relationship to vaccination) during 4-day follow-up period was calculated per group with exact 95% CI. Specific follow-up of solicited general symptoms fever and rash/exanthema was performed for subjects in Group 1 and 2 over the 42-day follow-up period. Report of extensive swellings were tabulated per group. Percentage of subjects with at least one report of an unsolicited adverse event, classified by WHO Preferred Term were tabulated per group with exact 95% CIs, during the 30-day follow-up. The same was tabulated for those determined to have a 'probable' or 'suspected' relationship to vaccination. SAEs reported during the study period were described.

Immunogenicity:

The analysis was performed on the ATP cohort. The distribution of antibody concentrations/ titres (anti-diphtheria, anti-tetanus, anti-PT, anti-FHA, anti-PRN, anti-HBs, anti-poliovirus types 1, 2 and 3, anti-PRP, anti-measles, anti-mumps, anti-rubella and anti-varicella antibodies) was calculated. Seropositivity/ seroprotection rates and Geometric Mean Concentrations/Titres (GMC/GMT) for antibodies against each component of the vaccines were calculated with 95% CI. The GMC/GMT calculations were performed by taking the anti-log of the mean of the log concentration/titre transformations. Vaccine response rates to each pertussis antigen (PT, FHA, PRN) were calculated with exact 95% CI. Reverse cumulative curves for antibody concentrations/titres at post-vaccination time point were plotted for all antibodies. The immune response to MMR was assessed only for subjects from Group 1 and the immune response to varicella was assessed only for subjects from Group 2. Immunogenicity of all other antigens was evaluated in all subjects.

SUMMARY-CONCLUSIONS:

The mean age of the total cohort was 15.9 months at the time of the booster vaccination, with a standard deviation of 1.73 months. The subjects were predominantly (93.7%) white.

Safety Results: (See synopsis Table 1)

Results show similar incidence of grade "3" symptom occurring within 4 days of vaccination in all three groups (28.8% of the subjects in Group 1, 25.0% of the subjects in Group 2 and 28.8% of the subjects in Group 3).

Redness at injection site was the most frequently reported symptom; 51.7% subjects in Group 1, 50% subjects in Group 2 and 55.9% subjects in Group 3. Redness at injection site was also the most frequently reported grade "3" symptom in Group 1 (13.8% subjects), swelling was the most frequently reported grade "3" symptom in Group 2 (8.9% of the subjects) and redness and swelling were the most frequently reported grade "3" symptom in Group 3 (both reported by 11.9% of the subjects). For five subjects (2 subjects each in Groups 1 and 2 and 1 subject in Group 3), extensive swelling was reported. None involved adjacent joints. Fever was the most frequently reported solicited general symptom in groups 1 and 2; 50% and 51.8% subjects respectively. In Group 3, irritability was the most frequently reported general symptom: 49.2% subjects. Fever was also the most frequently reported grade "3" solicited general symptom in Group 1 and Group 2 (reported by 8.6% and 5.4% subjects respectively). In Group 3 however, loss of appetite was the most frequently reported grade "3" symptom: 5.1% subjects. During the 42-day follow-up period there were no reports of measles/rubella like or varicella like rash in Groups 1 and 2. Seventy-six subjects out of 173 (26 subjects each in groups 1 and 2 and 24 subjects in group 3) reported at least one unsolicited symptom, but only seven subjects reported at least one unsolicited symptom with a 'probable' or 'suspected' relationship to the vaccination.

Serious Adverse Events: Only one subject (n° 224 in Group 1) reported an SAE in this booster study. The investigator determined the SAE as not related to the booster vaccination.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium Name of Finished Product: Infanrix™ hexa, Priorix™ and Varilrix™ Name of active substance: Diphtheria and tetanus toxoids, PT, PRN, FHA, HBsAg, poliovirus types 1, 2, 3, PRP Live attenuated measles, mumps, rubella vaccine Live attenuated varicella vaccine	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

Synopsis Table 1: Incidence of solicited symptoms and grade "3" solicited symptoms during the 4-day follow-up (ATP reactogenicity cohort)

		Group 1 (N = 58)			Group 2 (N = 56)			Group 3 (N = 59)		
		%	95% CI		%	95% CI		%	95% CI	
Any Symptoms*										
	Total	86.2	74.6	93.9	82.1	69.6	91.1	79.7	67.2	89.0
	Grade "3"	28.8	17.8	42.1	25.0	14.4	38.4	28.8	17.8	42.1
Solicited Local Symptom										
Pain	Total	39.7	27.0	53.4	30.4	18.8	44.1	47.5	34.3	60.9
	Grade "3"	1.7	0.0	9.2	7.1	2.0	17.3	5.1	1.1	14.1
Redness	Total	51.7	38.2	65.0	50.0	36.3	63.7	55.9	42.4	68.8
	Grade "3"	13.8	6.1	25.4	5.4	1.1	14.9	11.9	4.9	22.9
Swelling	Total	43.1	30.2	56.8	26.8	15.8	40.3	39.0	26.5	52.6
	Grade "3"	12.1	5.0	23.3	8.9	3.0	19.6	11.9	4.9	22.9
Solicited General Symptoms										
Drowsiness	Total	43.1	30.2	56.8	30.4	18.8	44.1	40.7	28.1	54.3
	Grade "3"	0.0	0.0	6.2	1.8	0.0	9.6	1.7	0.0	9.1
Irritability	Total	44.8	31.7	58.5	35.7	23.4	49.6	49.2	35.9	62.5
	Grade "3"	0.0	0.0	6.2	1.8	0.0	9.6	3.4	0.4	11.7
Loss of appetite	Total	32.8	21.0	46.3	30.4	18.8	44.1	27.1	16.4	40.3
	Grade "3"	3.4	0.4	11.9	1.8	0.0	9.6	5.1	1.1	14.1
Fever (rectal)	≥ 38.0 °C	50.0	36.6	63.4	51.8	38.0	65.3	42.4	29.6	55.9
	> 39.5 °C	8.6	2.9	19.0	5.4	1.1	14.9	3.4	0.4	11.7

Group 1: DTPa-HBV-IPV/Hib + Priorix™ ; Group 2: DTPa-HBV-IPV/Hib + Varilrix™ ; Group 3: DTPa-HBV-IPV/Hib
*: solicited or unsolicited; N: total number of subjects with at least one documented dose
n (%): number (percentage) of subjects presenting at least one type of solicited symptom
95% CI: Exact 95% confidence interval, lower and upper limit
Grade "3" pain: cried when the limb was moved/spontaneously painful
Grade "3" redness or swelling: redness or swelling > 20 mm at the injection site
Grade "3" drowsiness: drowsiness that prevented normal activities
Grade "3" irritability: crying that could not be comforted/prevented normal activities
Grade "3" loss of appetite: had not eaten at all

Immunogenicity Results: (See synopsis Table 2)

Immunogenicity analyses were based on the ATP cohort.

One month after vaccination,

- At least 96% of subjects in all groups had seroprotective antibody concentrations/ titres in terms of anti-tetanus, anti-diphtheria, anti-HBs, anti-poliovirus types 1, 2, 3 and anti-PRP antibodies.
- The vaccine response to the pertussis antigen ranged between 87.8-98.1% in all three groups. All seronegative subjects responded to anti-FHA and anti-PT antibodies at post-vaccination time point. All but one seronegative subject in Group 1 responded to anti-PRN antibodies at post-vaccination time point.
- 94.5% of subjects in Group 1 were seroprotected against measles and 96.4% against rubella. 88.2% of subjects in Group 1 were seropositive to anti-mumps antibodies.
- 97.8% of subjects in Group 2 were seropositive to anti-varicella antibodies.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium Name of Finished Product: Infanrix™ hexa, Priorix™ and Varilrix™ Name of active substance: Diphtheria and tetanus toxoids, PT, PRN, FHA, HBsAg, poliovirus types 1, 2, 3, PRP Live attenuated measles, mumps, rubella vaccine Live attenuated varicella vaccine	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

Synopsis Table 2: Seropositivity/seroprotection/Vaccine response rates and GMTs/GMCs after the booster vaccination (ATP immunogenicity cohort)

Antibody (Cut-off)	Group	N	%	95% CI		GMC/GMT	95% CI	
Anti-Diphtheria (≥ 0.1 IU/ml)	1	55	98.2	90.3	100.0	4.129	2.891	5.897
	2	50	98.0	89.4	99.9	3.955	2.798	5.591
	3	52	100.0	93.2	100.0	4.410	3.456	5.626
Anti-Tetanus (≥ 0.1 IU/ml)	1	55	98.2	90.3	100.0	5.724	4.258	7.693
	2	50	98.0	89.4	99.9	4.742	3.510	6.408
	3	52	100.0	93.2	100.0	5.281	4.072	6.849
Anti-PT Vaccine response	1	55	92.7	82.4	98.0	123.5	95.7	159.5
	2	50	90.0	78.2	96.7	105.6	79.4	140.3
	3	52	96.1	86.5	99.5	131.3	105.0	164.2
Anti-FHA Vaccine response	1	55	90.9	80.0	97.0	463.3	357.5	600.5
	2	49	87.8	75.2	95.4	480.3	383.4	601.7
	3	52	98.1	89.7	100.0	602.4	507.2	715.5
Anti-PRN Vaccine response	1	55	92.7	82.4	98.0	431.1	294.6	630.8
	2	50	90.0	78.2	96.7	289.9	217.6	386.3
	3	52	96.2	86.8	99.5	372.3	281.2	493.0
Anti-HBs (≥ 10 mIU/ml)	1	55	96.4	87.5	99.6	4779.0	2693.4	8479.5
	2	50	100.0	92.9	100.0	4792.5	2875.0	7989.0
	3	52	100.0	93.2	100.0	3838.7	2301.6	6402.3
Anti-poliovirus type 1 (≥ 8 fold-dilution)	1	48	100.0	92.6	100.0	1477.7	978.1	2232.5
	2	48	100.0	92.6	100.0	1385.6	956.9	2006.5
	3	52	100.0	93.2	100.0	1408.5	993.2	1997.5
Anti-poliovirus type 2 (≥ 8 fold-dilution)	1	48	100.0	92.6	100.0	1901.8	1337.5	2704.3
	2	48	100.0	92.6	100.0	1683.4	1237.7	2289.8
	3	50	100.0	92.9	100.0	1684.5	1269.0	2236.1
Anti-poliovirus type 3 (≥ 8 fold-dilution)	1	49	100.0	92.7	100.0	3921.3	2977.7	5164.0
	2	45	100.0	92.1	100.0	3757.7	3016.1	4681.8
	3	51	100.0	93.0	100.0	3742.2	2728.0	5133.6
Anti-PRP (≥1 µg/ml)	1	55	98.2	90.3	100.0	72.865	47.715	111.271
	2	50	100.0	92.9	100.0	70.855	51.522	97.443
	3	52	100.0	93.2	100.0	63.920	43.529	93.864
Anti-measles (150 mIU/ml)	1	55	94.5	84.9	98.9	2705.6	2004.6	3651.6
Anti-mumps (231 U/ml)	1	51	88.2	76.1	95.6	858.7	635.2	1160.7
Anti-rubella (4 IU/ml)	1	53	96.4	87.5	99.6	58.3	44.5	76.2
Anti-varicella (1: 4 dilution)*	2	46	97.8	88.5	99.9	158.1	115.6	216.1

Group 1: DTPa-HBV-IPV/Hib + Priorix™; Group 2: DTPa-HBV-IPV/Hib + Varilrix™
Group 3: DTPa-HBV-IPV/Hib; GMC/T: Geometric mean concentration/titre
N: number of subjects with available results
%: percentage of subjects with titres ≥ assay cut off; 95% CI: exact 95% confidence interval
Vaccine response:
for subjects who were seronegative at pre-vaccination: appearance of pertussis antibodies;
for subjects who were seropositive at pre-vaccination: at least two-fold increase in pre-vaccination antibody titres
*: in order to be consistent with GSK Biologicals' MMR and varicella vaccine studies, a cut-off of ¼ was used

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium Name of Finished Product: Infanrix™ hexa, Priorix™ and Varilrix™ Name of active substance: Diphtheria and tetanus toxoids, PT, PRN, FHA, HBsAg, poliovirus types 1, 2, 3, PRP Live attenuated measles, mumps, rubella vaccine Live attenuated varicella vaccine	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

Conclusions:

- The conclusions from this study must be considered with caution due to the small sample size.
- The incidence of all solicited local symptoms and of drowsiness, irritability and loss of appetite in terms of solicited general symptoms were similar between the three groups.
- A higher incidence of grade "3" fever (rectal temperature > 39.5 °C) during the 4 days following vaccination was observed in the two co-administration groups; with 8.6% and 5.4% incidence as compared to 3.4% after DTPa-HBV-IPV/Hib alone. In view of another co-administration study with a vaccine of the same family (MMRV), the incidences observed in the group receiving DTPa-HBV-IPV/Hib + MMR (8.6%) appear as unusually high.
- A peak of fever was observed in the MMR recipients at the beginning of the second week after vaccination. This peak is classically described in MMR vaccinees.
- The co-administration of Priorix™ or Varilrix™ with Infanrix™ hexa given as a booster dose in the second year of life did not seem to affect the immune response to the various vaccine antigens. However, it should be noted that the seroconversion rate (88.2%) to the mumps component observed in this trial was at the lower end of the range of the seroconversion rates previously reported (83.3-100.0%). It must also be noted that in this trial no direct comparison to the administration of Priorix™ alone was made and given the low numbers of subjects evaluated in the immunogenicity analysis it is not possible to draw any definitive conclusions.

Date of report: 27 August 2004

Document 1

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium Name of Finished Product: *Havrix*™ Name of active substance: Diphtheria and tetanus toxoids, PRP, PT, PRN, FHA, polio type 1, 2, 3 and HBsAg, inactivated hepatitis A	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

Title of the study:
Open, randomized, multicentre, phase III clinical trial to assess the reactogenicity and immunogenicity of a booster dose of GSK Biologicals' DTPa-HBV-IPV/Hib vaccine, co-administered during the same visit with GSK Biologicals' HAV vaccine (*Havrix*™), in children in their second year of life, previously vaccinated in the DTPa-HBV-IPV-039, -041, -043 or -057 primary vaccination studies (CPMS N° 217744/039, 041, 043 or 057).

Principal Investigator: s22 [redacted]

Study Center: This study was performed at 10 centers in Germany.

Publication (reference): Not published as of 28 November 2003.

Study period: Date of first visit: 16 November 1999
Date of last visit: 29 June 2000 (Group 2)
27 December 2000 (Group 1)

Clinical phase: III

Objectives:
Primary:
- To assess the reactogenicity of the study vaccines in terms of grade "3" local or general, solicited or unsolicited symptoms occurring within 4 days following vaccination.

Secondary:
- To assess the safety and reactogenicity of the study vaccines in terms of solicited symptoms, unsolicited symptoms and serious adverse events.
- To assess the immune response to the study vaccines.
- To assess the persistence of antibodies to all the antigens contained in GSK Biologicals' combined DTPa-HBV-IPV/Hib vaccine prior to booster vaccination.

Methodology:
Study design: open, multicentric (10 centres) booster study with a random balanced (1:1) allocation into two parallel groups of healthy children aged ≥ 12 and < 24 months at the time of booster vaccination:
- Group 1 received DTPa-HBV-IPV/Hib + *Havrix*™ followed by a second dose of *Havrix*™, 6 months later.
- Group 2 received DTPa-HBV-IPV/Hib as control.

Two or three blood samples were taken for Group 1: one immediately before Dose 1 (DTPa-HBV-IPV/Hib + *Havrix*™), one (optional) approximately 1 month after Dose 1 and one approximately 1 month after the second dose of *Havrix*™. Two blood samples were taken for Group 2: one immediately before Dose 1 and one approximately 1 month after this first dose.

Number of subjects:
Planned: 100 Enrolled: 82 (41 in each group) Completed: 78 (Group 1: 38, Group 2: 40)
Analyzed for safety (ATP): 82 (Group 1: 41, Group 2: 41)
Analyzed for immunogenicity (ATP): 71 (Group 1: 37, Group 2: 34)

Diagnosis and criteria for inclusion:
Healthy male or female children ≥ 12 and < 24 months of age, having completed a 3-dose primary vaccination course as part of either of studies DTPa-HBV-IPV-039, -041, -043 or -057, and for whom written informed consent was obtained from the parent/guardian before the start of the study.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium Name of Finished Product: *Havrix*™ Name of active substance: Diphtheria and tetanus toxoids, PRP, PT, PRN, FHA, polio type 1, 2, 3 and HBsAg, inactivated hepatitis A	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** Volume: Page:	(for national authority only)

Test product, dose, mode of administration, lot No.:

Vaccination schedule/site: Group 1 received DTPa-HBV-IPV and Hib vaccines combined in one injection, administered as an intramuscular injection in the left antero-lateral thigh and *Havrix*™ in the right antero-lateral thigh, at ≥ 12 and < 24 months of age. This group also received a second dose of *Havrix*™ after six months.

Vaccine/composition/dose/lot number: **GlaxoSmithKline (GSK) Biologicals' combined DTPa-HBV-IPV vaccine** contained (per 0.5 ml dose): ≥ 30 IU (25 Lf) diphtheria toxoid, ≥ 40 IU (10 Lf) tetanus toxoid, 25 µg pertussis toxoid (PT), 25 µg filamentous haemagglutinin (FHA), 8 µg pertactin (PRN), 10 µg recombinant hepatitis B surface antigen (HBsAg), 40 D antigen units of poliovirus type 1, 8 D antigen units of poliovirus type 2, 32 D antigen units of poliovirus type 3, 150 mM sodium chloride, ≤ 100 µg formalin, ≤ 25 µg neomycin sulphate, ≤ 50 µg polysorbate, 0.7 mg aluminium and ≤ 2.5 mg phenoxyethanol. Lot number: D21799B2.

GSK Biologicals' *Haemophilus influenzae* type b (Hib) adsorbed vaccine contained (per 0.5 ml dose after reconstitution): 10 µg poly-ribosyl-ribitol phosphate (PRP), 20-40 µg tetanus toxoid, 0.12 mg aluminium and 12.6 mg lactose. Lot number: DHIB200A41.

GSK Biologicals' inactivated hepatitis A vaccine (*Havrix*™) vaccine contained (per 0.5 ml dose): 720 EL.U HAV (Strain HM 175) and 0.25 mg aluminium. Lot number: VHA580B9

Reference therapy, dose and mode of administration, batch number:

Vaccination schedule/site: Group 2 received DTPa-HBV-IPV and Hib vaccines combined in one injection, administered as an intramuscular injection in the left antero-lateral thigh.

Vaccine/composition/dose/lot number: Same as for Group 1 for DTPa-HBV-IPV and Hib vaccines.

Duration of treatment: 7 months per subject for Group 1 & 1 month per subject for Group 2.

Criteria for evaluation:

Primary endpoint:

- Occurrence of any grade "3" symptoms within 4 days after vaccination, at Visit 1.

Secondary endpoints:

- Occurrence and intensity of solicited local symptoms within 4 days after vaccination.
- Occurrence, intensity and relationship to vaccination of solicited general symptoms within 4 days after vaccination.
- Occurrence, intensity and relationship to vaccination of unsolicited symptoms within 30 days after vaccination.
- Occurrence, intensity and relationship to vaccination of Serious Adverse Events (SAE) throughout the study period, up to and including 30 days post-vaccination.

Immunogenicity prior to booster vaccination, one month after vaccine Dose 1 (optional for Group 1), and one month after the second dose of HAV (Group 1 only):

- Anti-diphtheria and anti-tetanus toxoid, anti-PT, anti-PRN, anti-FHA, anti-PRP, anti-HBs and anti-poliovirus types 1, 2 and 3 (both groups), and anti-HAV (Group 1 only) antibody concentrations/titres.
- Seroprotection status:
  - anti-PRP antibody concentration ≥ 0.15 µg/ml and ≥ 1.0 µg/ml
  - anti-diphtheria toxoid antibody concentration ≥ 0.1 IU/ml
  - anti-tetanus toxoid antibody concentration ≥ 0.1 IU/ml
  - anti-poliovirus type 1 antibody titre ≥ 8
  - anti-poliovirus type 2 antibody titre ≥ 8
  - anti-poliovirus type 3 antibody titre ≥ 8
  - anti-HBs antibody concentration ≥ 10 mIU/ml

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium Name of Finished Product: *Havrix*™ Name of active substance: Diphtheria and tetanus toxoids, PRP, PT, PRN, FHA, polio type 1, 2, 3 and HBsAg, inactivated hepatitis A	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

- Seropositivity status:
  - anti-PT antibody concentration ≥ 5 EL.U/ml
  - anti-PRN antibody concentration ≥ 5 EL.U/ml
  - anti-FHA antibody concentration ≥ 5 EL.U/ml
  - anti-HAV antibody concentration ≥ 33 mIU/ml (Group 1 only)
- Booster vaccination response (after dose 1 only) to PT, PRN and FHA one month after the booster dose, defined as appearance of antibodies in subjects who were initially seronegative or at least a 2-fold increase in antibody concentrations between pre-booster and post-booster vaccination in subjects who were initially seropositive.

Statistical methods:

Safety: The percentage of subjects reporting any grade "3" symptom, at least one grade "3" local or at least one grade "3" general symptom after each dose was calculated per group with exact 95% confidence interval (CI). The incidence of individual solicited symptoms within the 4-day follow-up period after each dose (solicited local, solicited general) were calculated per group with exact 95% CI. The number and percentage of subjects with at least one report of an unsolicited adverse event, classified by WHO Preferred Term were tabulated per group with exact 95% CIs, for all reports within the 30-day follow-up after each dose and for those determined to have a 'possible' or 'suspected' relationship to vaccination. SAEs were described.

Immunogenicity: Seropositivity/ seroprotection rates and Geometric Mean Concentrations/Titres (GMC/GMT) for each component of the vaccines were calculated with 95% CI. The GMC/GMT calculations were performed by taking the anti-log of the mean of the log concentration/titre transformations. Vaccine response rates to each pertussis antigen (PT, FHA, PRN) were calculated with exact 95% CI. Reverse cumulative curves for antibody concentrations/titres at post-vaccination time point for all antibodies were plotted. The distribution of antibody concentrations/titres for all antibodies was calculated.

SUMMARY-CONCLUSIONS:

Demographics: The mean age of the total cohort was 16.8 months at the time of booster vaccination with a standard deviation of 3.15 months.

Safety Results: The co-administration of *Havrix*™ and *INFANRIX*™ *hexa* as a booster dose in the second year of life did not increase the overall incidence of symptoms reported as compared to *INFANRIX*™ *hexa* administered alone. However, concerning the primary objective (any grade "3" symptoms), 24.4% of the subjects in Group 1 and 34.1% of the subjects in Group 2 reported at least one grade "3" symptom occurring within 4 days after the booster dose. Although this higher incidence in Group 2 is unexpected, it is important to note that the 95% confidence intervals are overlapping and that due to the small sample size, no conclusions can be drawn.

Redness at the injection site was the most frequently reported solicited local and solicited local grade "3" symptom in both groups during the 4-day follow-up period after booster vaccination. Fever was the most frequently reported solicited general symptom in both groups and the most frequently reported grade "3" general symptom in Group 2. Drowsiness was the most frequently reported grade "3" general symptom in Group 1.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium Name of Finished Product: *Havrix*™ Name of active substance: Diphtheria and tetanus toxoids, PRP, PT, PRN, FHA, polio type 1, 2, 3 and HBsAg, inactivated hepatitis A	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

Table 1: Incidence of solicited symptoms and grade "3" symptoms during the 4-day follow-up (ATP reactogenicity cohort)

		Group 1 (N = 41)				Group 2 (N = 41)			
		n	%	95% CI		n	%	95% CI	
Any symptom*									
	Total	32	78.0	62.4	89.4	34	82.9	67.9	92.8
	Grade "3"	10	24.4	12.4	40.3	14	34.1	20.1	50.6
Solicited Local Symptom									
Pain	Total	20	48.8	32.9	64.9	17	41.5	26.3	57.9
	Grade "3"	2	4.9	0.6	16.5	2	4.9	0.6	16.5
Redness	Total	24	58.5	42.1	73.7	21	51.2	35.1	67.1
	Grade "3"	4	9.8	2.7	23.1	7	17.1	7.2	32.1
Swelling	Total	17	41.5	26.3	57.9	16	39.0	24.2	55.5
	Grade "3"	4	9.8	2.7	23.1	2	4.9	0.6	16.5
Solicited General Symptoms									
Drowsiness	Total	13	31.7	18.1	48.1	16	39.0	24.2	55.5
	Grade "3"	2	4.9	0.6	16.5	0	0.0	0.0	8.6
Irritability	Total	15	36.6	22.1	53.1	13	31.7	18.1	48.1
	Grade "3"	0	0.0	0.0	8.6	0	0.0	0.0	8.6
Loss of appetite	Total	12	29.3	16.1	45.5	11	26.8	14.2	42.9
	Grade "3"	1	2.4	0.1	12.9	0	0.0	0.0	8.6
Fever	≥ 38.0 °C	18	43.9	28.5	60.3	16	39.0	24.2	55.5
	> 39.5 °C	1	2.4	0.1	12.9	5	12.2	4.1	26.2

Group 1: DTPa-HBV-IPV/Hib + *Havrix*™ (+ *Havrix*™ 6 months later); Group 2: DTPa-HBV-IPV/Hib
* = solicited or unsolicited; N = total number of subjects with at least one documented dose
n (%) = number (percentage) of subjects presenting at least one type of solicited symptom
Grade "3" pain = cried when the limb was moved/spontaneously painful
Grade "3" redness or swelling = redness or swelling > 20 mm at the injection site
Grade "3" drowsiness = drowsiness that prevented normal activities
Grade "3" loss of appetite = not eating at all
Grade "3" irritability = crying or protesting that could not be comforted/prevented normal activities
Fever = rectal temperature; 95% CI = Exact 95% confidence interval, lower and upper limits

The high incidence of fever > 39.5°C in the group that received *INFANRIX*™ *hexa* alone seems to be purely coincidence, as the incidence in the group that received *INFANRIX*™ *hexa* co-administered with *Havrix*™ (2.4%) was more in line with the incidence of grade "3" fever previously reported following a booster dose of *INFANRIX*™ *hexa*. Due to the small sample size, and given that the 95%CI are overlapping, no conclusions can be drawn.
Following the booster dose, 26 (13 in each group) of the 82 subjects reported at least one unsolicited symptom but only 1 of them (in Group 2) had symptoms with a 'probable' or 'suspected' relationship to vaccination.
Serious Adverse Events: Two SAEs (subject n° 18 and n° 27 in Group 1) were reported during the study period and both were determined by the investigator to be 'not related' to vaccination.

Document 1

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium Name of Finished Product: *Havrix*™ Name of active substance: Diphtheria and tetanus toxoids, PRP, PT, PRN, FHA, polio type 1, 2, 3 and HBsAg, inactivated hepatitis A	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Immunogenicity Results:

Table 2: Seropositivity/seroprotection/Vaccine response rates and GMCs/GMTs one month after the booster vaccination (ATP immunogenicity cohort)

Antibody Cut-off	Group	N	%	95% CI		GMC/GMT Value	95% CI	
Anti-diphtheria	1	11	90.9	58.7	99.8	2.946	0.941	9.224
≥ 0.1 IU/ml	2	34	100.0	89.7	100.0	3.016	2.076	4.380
Anti-tetanus	1	11	90.9	58.7	99.8	4.426	1.318	14.862
≥ 0.1 IU/ml	2	34	100.0	89.7	100.0	5.517	3.685	8.261
Anti-PT	1	11	90.9	58.7	99.8	87.2	34.2	221.9
Vaccine Response	2	34	94.1	80.3	99.3	102.1	78.7	132.4
Anti-FHA	1	11	90.9	58.7	99.8	369.6	168.7	809.6
Vaccine Response	2	32	93.8	79.2	99.2	468.9	369.5	595.0
Anti-PRN	1	11	90.9	58.7	99.8	398.6	163.0	975.1
Vaccine Response	2	34	97.1	84.7	99.9	420.0	302.2	583.8
Anti-HBs	1	11	100.0	71.5	100.0	5910.6	1464.3	23857.1
≥ 10 mIU/ml	2	31	97.1	84.7	99.9	4604.2	2179.9	9724.8
Anti-poliovirus type 1	1	10	100.0	69.2	100.0	1606.2	474.1	5441.5
≥ 8	2	29	100.0	88.1	100.0	1553.8	924.4	2611.5
Anti- poliovirus type 2	1	10	100.0	69.2	100.0	2696.1	863.5	8417.9
≥ 8	2	30	100.0	88.4	100.0	1887.3	1218.5	2923.3
Anti- poliovirus type 3	1	10	100.0	69.2	100.0	3425.5	930.7	12607.8
≥ 8	2	30	100.0	88.4	100.0	3361.0	2339.7	4828.1
Anti-PRP	1	11	100.0	71.5	100.0	45.212	11.103	184.106
≥ 0.15 µg/ml	2	34	100.0	89.7	100.0	59.352	36.645	96.131
Anti-HAV ≥ 33 mIU/ml								
Post-dose 1 (M1)	1	11	72.7	39.0	94.0	61.615	28.090	135.152
Post-dose 2 (M7)	1	34	100.0	89.7	100.0	1638.43	1115.76	2405.95

Group 1: DTPa-HBV-IPV/Hib + *Havrix*™ (+ *Havrix*™ 6 months later); Group 2: DTPa-HBV-IPV/Hib
N = number of subjects with available results one month after the booster vaccination (for vaccine response to pertussis antigens this represents the number of subjects with both pre- and post-vaccination immunogenicity results available)
VR = Vaccine response
% = percentage of subjects with titres within the specified range or with a vaccine response for the pertussis antigen
95% CI = 95% Confidence Interval
GMC/T = Geometric Mean Concentration/Titre
Post (M1) = One month after the booster vaccination
Post (M7) = One month after the second dose of *Havrix*™

One month after the booster dose,

- All subjects, except one in Group 1, had seroprotective antibody titres for anti-tetanus, anti-diphtheria, anti-HBs, anti-polio types 1, 2, 3 and anti-PRP antibodies.
- Over 90% of the subjects showed a booster response against PT, FHA and PRN.
- Eight out of 11 subjects in Group 1 were seropositive for anti-HAV antibodies.

One month after the second dose of *Havrix*™,

- All subjects in Group 1 were seropositive for anti-HAV antibodies with a substantial increase in anti-HAV GMCs compared to those measured one month after the first dose of *Havrix*™.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product**: *Havrix*™ **Name of active substance**: Diphtheria and tetanus toxoids, PRP, PT, PRN, FHA, polio type 1, 2, 3 and HBsAg, inactivated hepatitis A	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Conclusions:

- Due to small sample size, conclusions should be considered with caution.
- The DTPa-HBV-IPV/Hib vaccine showed an acceptable safety and reactogenicity profile when given as a booster dose in the second year of life.
- Co-administration of *Havrix*™ and *INFANRIX*™ *hexa* given as a booster dose in the second year of life did not seem to interfere with the immune responses to any of the *INFANRIX*™ *hexa* vaccine antigens.
- Eight out of 11 subjects seroconverted for hepatitis A following the first dose of Havrix co-administered with *INFANRIX*™ *hexa* in the second year of life, and all subjects tested for anti-HAV antibodies following the second dose of *Havrix* were seropositive, with a substantial increase in anti-HAV GMC.

Date of report: 28 November 2003 (Final)

Document 1

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium Name of Finished Product: *Infanrix HeXa* , *Infanrix* -IPV+Hib and *Engerix-B Kinder* Name of active substance: Diphtheria and tetanus toxoids, PRP, PT, PRN, FHA, poliovirus types 1, 2, 3 and HBsAg	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Title of the study: 217744/074 (DTPaHBV-IPV-074)
Open, randomized, multicenter, phase IIIb clinical trial to assess the incidence of high grade fever (≥ 40.0°C) within 4 days following a booster dose in the second year of life of GlaxoSmithKline (GSK) Biologicals' combined DTPa-HBV-IPV/Hib vaccine (*Infanrix HeXa*) as compared to GSK Biologicals' combined DTPa-IPV/Hib (*Infanrix* -IPV+Hib) and HBV (*Engerix-B* Kinder) vaccines administered concomitantly in separate injections to children previously primed with licensed vaccines according to the vaccination recommendations currently in place in Germany.

Principal Investigator: s22 [redacted]

Study Centers: Multiple centers in Germany

Publication (reference): Not published as of 11 June 2002.

Study period:
Date of first visit: 18 September, 2000
Date of last visit (active phase): 23 August, 2001
Date of last visit (safety follow-up phase): 01 February 2002

Clinical phase: IIIb

Objectives:

Primary:

To assess and compare the incidence of high grade fever (≥ 40.0 °C) within 4 days after booster vaccination with DTPa-HBV-IPV/Hibor DTPa-IPV/Hiband HBV.

Secondary:

- To assess the use of antipyretic medication within 4 days after booster vaccination
- To assess the incidence of convulsions occurring within 4 days after booster vaccination
- To assess the incidence of emergency room visits and hospitalizations occurring within 4 days after booster vaccination
- To assess the incidence and causal relationship to vaccination of serious adverse events (SAEs) occurring within the first 30 days after booster vaccination and up to and including 6 months after booster vaccination
- To assess the incidence of large local injection site reactions within 4 days after booster vaccination and causing concern to the vaccinees parents/guardians (local injection site swelling with diameter > 50 mm, noticeable diffuse injection site swelling or noticeable increased circumference of the injected limb).

Methodology:
Study design: Open, multicentric, randomized study with two parallel groups with a balanced allocation (ratio 1:1)

- Group 1 received GSK Biologicals' combined DTPa-HBV-IPV/Hib vaccine
- Group 2 (control) received GSK Biologicals' combined DTPa-IPV/Hib vaccine and HBV vaccine

Number of subjects:
Planned: 7800
Completed active phase: 8000
Completed safety follow-up: 8006
Enrolled: 8050 (4032 in Group 1, 4018 in Group 2)
ATP cohort for safety: 7908 (3964 in Group 1, 3944 in Group 2)

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** *Infanrix HeXa* , *Infanrix* -IPV +Hib and *Engerix-B Kinder* **Name of active substance:** Diphtheria and tetanus toxoids, PRP, PT, PRN, FHA, poliovirus types 1, 2, 3 and HBsAg	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Diagnosis and criteria for inclusion:
Healthy male or female toddlers in their second year of life, having received a complete primary vaccination course against diphtheria, tetanus, pertussis, hepatitis B, polio and Hib disease, with licensed vaccines according to the vaccination recommendations in place in Germany at the time the study was conducted. Written informed consent must have been provided from the parents or guardians of the subject.

Test product, dose, mode of administration, lot No.:
Vaccination schedule/site: Subjects in Group 1 received a booster dose of GSK Biologicals' combined DTPa-HBV-IPV/Hib vaccine administered intra-muscularly (IM) in the left anterolateral thigh in their second year of life.
Vaccine/composition/dose/lot number:
GSK Biologicals' DTPa-HBV-IPV vaccine containing per 0.5 ml dose: ≥ 30 IU (25 Lf) diphtheria toxoid, ≥ 40 IU (10 Lf) tetanus toxoid, 25 mcg pertussis toxoid (PT), 25 mcg filamentous hemagglutinin (FHA), 8 mcg pertactin (PRN), 10 mcg hepatitis B surface antigen (HBsAg) (recombinant), 40 D antigen units poliovirus type 1, 8 D antigen units poliovirus type 2, 32 D antigen units poliovirus type 3, ≤ 2.5 mg 2-phenoxyethanol and 0.7 mg Aluminium as salt. Lot no.: 21833A9
GSK Biologicals' *Haemophilus influenzae* type b (Hib) conjugate vaccine containing per dose (after reconstitution): 10 mcg polyribosyl ribitol phosphate (PRP), 20-40 mcg tetanus toxoid, 10 mg Lactose and 0.12 mg Aluminium as salt. Lot no.: Hib407A47

Reference therapy, dose and mode of administration, batch number:
Vaccination schedule/site: Subjects in Group 2 received GSK Biologicals' combined DTPa-IPV/Hib vaccine administered IM in the left anterolateral thigh concomitantly with HBV vaccine administered IM in the right anterolateral thigh in their second year of life.
Vaccine/composition/dose/lot number:
GSK Biologicals' DTPa-IPV vaccine containing per 0.5 ml dose: ≥ 30 IU (25 Lf) diphtheria toxoid, ≥ 40 IU (10 Lf) tetanus toxoid, 25 mcg PT, 25 mcg FHA, 8 mcg PRN, 40 D antigen units poliovirus type 1, 8 D antigen units poliovirus type 2, 32 D antigen units poliovirus type 3, ≤ 2.5 mg 2-phenoxyethanol and 0.5 mg Aluminium as salt. Lot no.: 20764B9A
GSK Biologicals' *Haemophilus influenzae* type b (Hib) conjugate vaccine containing per dose (after reconstitution): 10 mcg PRP, 20-40 mcg tetanus toxoid and 10 mg Lactose. Lot no.: Hib308B47A
GSK Biologicals' *Engerix-B™ Kinder* vaccine containing per 0.5 ml dose: 10 mcg recombinant hepatitis B surface antigen (HBsAg), 0.25 mg Aluminium as salt. Lot no.: ENG3170C9

Duration of treatment: Duration of study approximately 1 month per subject with a safety follow-up of approximately 6 months.

Criteria for evaluation:
Primary:
Recording of high grade fever (≥ 40.0 °C) by the parents/guardians during a 4-day follow-period after booster vaccination

Name of Company: GlaxoSmithKline Biologicals. Rixensart, Belgium Name of Finished Product: *Infanrix HeXa* , *Infanrix* -IPV +Hib and *Engerix-B Kinder* Name of active substance: Diphtheria and tetanus toxoids, PRP, PT, PRN, FHA, poliovirus types 1, 2, 3 and HBsAg	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Secondary:

Recording of anti-pyretic medication use during a 4-day follow-period after booster vaccination by the parents/guardians.

Recording of convulsions, emergency room visits, hospitalizations and large local injection site reactions (defined as local injection site swelling with diameter > 50 mm, noticeable diffuse injection site swelling or noticeable increased circumference of the injected limb) occurring during a 4-day follow-period after booster vaccination.

Recording of serious AEs including intensity and relationship to vaccination throughout the study (during the first 30 days after booster vaccination and up to and including 6 months post-booster vaccination)

Statistical methods:

Immunogenicity: Not applicable.

Safety:

Descriptive analysis: The percentage of subjects having reported symptoms after vaccination and their exact 95% confidence interval (CI) were computed by group according to the type of symptoms, their intensity and relationship to vaccination. The difference between groups was evaluated with a two-sided Fisher exact test. Likewise the percentage of subjects having used anti-pyretic medication within the 4 days post-vaccination was evaluated.

Inferential analysis:

For the percentages of subjects having reported high grade fever (≥ 40.0°C) a two-sided Fisher exact p-value below 0.1 was to be considered as evidence for a difference between groups.

In response to comments received from CPMP upon review of the protocol, the evaluation of 95% CIs for group differences was added to the analysis. An upper limit of the 95% CI for the group difference in the incidence of high grade fever (≥ 40.0°C) below 0.8% was deemed acceptable by the reviewers.

SUMMARY-CONCLUSIONS :

Safety Results:

Synopsis Table 1: Incidences of solicited fever, use of antipyretics, and convulsions within 4 days after booster vaccination (ATP cohort for safety)*

Endpoint	Group 1 N = 3964		Group2 N = 3944		Difference (Group 1– Group 2)	95% CI		Two sided p-value#
	n	%	n	%				
Within 4 days after booster vaccination								
Fever ≥ 40°C§	25	0.6	25	0.6	-0.00	-0.44	0.43	1.000
Fever ≥ 39.5°C	98	2.5	110	2.8	-0.32	-1.11	0.47	0.399
Fever ≥ 39.0°C	251	6.3	254	6.4	-0.11	-1.27	1.05	0.854
Fever ≥ 38.5°C	648	16.3	589	14.9	1.41	0.24	3.11	0.089
Fever ≥ 38.0°C	1479	37.3	1350	34.2	3.08	0.94	5.26	0.005
Fever ≥ 38.0°C requiring medical attention	234	5.9	171	4.3	1.57	0.54	2.65	0.002
Use of anti-pyretics	433	10.9	410	10.4	0.53	-0.89	1.99	0.466
Convulsions (febrile or afebrile)	0	0.0	2	0.1	-0.05	-0.25	0.12	0.249

For table notes see next page

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium Name of Finished Product: *Infanrix HeXa* , *Infanrix* -IPV +Hib and *Engerix-B Kinder* Name of active substance: Diphtheria and tetanus toxoids, PRP, PT, PRN, FHA, poliovirus types 1, 2, 3 and HBsAg	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

Group 1 received GSK Biologicals' DTPa-HBV-IPV/Hib
Group 2 received GSK Biologicals' DTPa-IPV/Hib + HBV
N = number of subjects with at least one symptom sheet completed
95% CI = exact 95% confidence interval; # Fisher exact test
n/% = number/percentage of subjects who reported the symptom of interest
Difference = Absolute risk difference
* fever measured via rectal route; § Primary endpoint

A small increase (1.41 to 3.08%) of the incidence of low grade fever (< 39°C) was observed following booster vaccination with DTPaHBV-IPV/Hib compared to the control group, but this was not considered as clinically relevant. With respect to the primary endpoint (fever ≥ 40.0°C), no statistically significant difference was observed and the upper limit of the 95% CI for the group difference was below the 0.8% limit, which was considered as acceptable by the CPMP reviewers.

Synopsis Table 2: Large injection site reactions (defined as local injection site swelling with diameter > 50 mm, noticeable diffuse injection site swelling or noticeable increased circumference of the injected limb) within 4 days after booster vaccination (ATP cohort for safety)

Endpoint	Group 1 N = 3964		Group 2 N = 3944		Difference (Group 1-Group 2)	95% CI		Two sided p-value#
	n	%	n	%				
Any large injection site reaction	101	2.5	83	2.1	0.44	-0.28	1.22	0.204
• Localized large swelling at the injection site	72	1.8	59	1.5				
• Diffuse swelling not involving adjacent joint	27	0.7	20	0.5				
• Extensive swelling reaction involving at least one adjacent joint	2	0.1	4	0.1				

Group 1 received GSK Biologicals' DTPa-HBV-IPV/Hib
Group 2 received GSK Biologicals' DTPa-IPV/Hib + HBV
N = number of subjects with at least one symptom sheet completed
95% CI = exact 95% confidence interval; # Fisher exact test
n/% = number/percentage of subjects who reported the symptom of interest
Difference = Absolute risk difference

Parents/guardians were instructed to contact the investigator immediately should their child manifest any symptoms that raised concern, including injection site swelling≥ 50 mm in diameter, diffuse swelling or a noticeable increase in limb circumference of the injected limb.

A small, statistically not significant increase (0.44%; p>0.1) of the incidence of large injection site reactions was observed following booster vaccination with DTPaHBV-IPV/Hib compared to the control group, but is not considered as clinically relevant. In addition to the large injection site reactions reported by subjects included in the ATP cohort for safety and presented in Synopsis Table 2, three additional subjects not included in the ATP cohort for safety also experienced large injection site reactions after booster vaccination with GSK Biologicals' DTPaHBV-IPV/Hib vaccine.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** *Infanrix HeXa* , *Infanrix* -IPV +Hib and *Engerix-B Kinder* **Name of active substance:** Diphtheria and tetanus toxoids, PRP, PT, PRN, FHA, poliovirus types 1, 2, 3 and HBsAg	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Synopsis Table 3: Serious adverse events following booster vaccination (ATP cohort for safety)

Endpoint	Group 1 N = 3964 n	%	Group 2 N = 3944 n	%	Difference (Group 1– Group 2)	95% CI		Two sided p-value#
Within 4 days after booster vaccination								
Emergency room visits and hospitalizations	3	0.1	8	0.2	-0.13	-0.40	0.12	0.145
SAEs causally related to vaccination	0	0.0	2	0.1	-0.05	-0.25	0.12	0.249
Within 30 days after booster vaccination								
Any SAEs	18	0.5	22	0.6	-0.10	-0.51	0.30	0.531
During the entire study period								
Any SAEs	104	2.6	74	1.9	0.75	0.03	1.51	0.028

Group 1 received GSK Biologicals' DTPa-HBV-IPV/Hib
Group 2 received GSK Biologicals' DTPa-IPV/Hib + HBV
N = number of subjects with at least one symptom sheet completed
95% CI= exact 95% confidence interval; # Fisher exact test
n/% = number/percentage of subjects who reported the symptom of interest
Difference = Absolute risk difference

No difference was observed between groups in terms of the incidence of SAEs reported within 4 or within 30 days following booster vaccination. Over the entire study period, 2.6% of subjects boosted with DTPa-HBV-IPV/Hib and 1.9% of subjects boosted in the control group reported an SAE. However none of the SAEs reported more than 4 days after booster vaccination were considered related to vaccination. In addition to the SAEs experienced by subjects included in the ATP cohort for safety and presented in Synopsis Table 3, four additional subjects not included in the ATP cohort for safety experienced SAEs after booster vaccination. None of these SAEs was regarded as causally related to vaccination. Two subjects reported SAEs within 4 or 30 days after vaccination with GSK Biologicals' DTPa-IPV/Hib + HBV, the remaining two subjects reported SAEs later than 30 days after vaccination with GSK Biologicals' DTPa-HBV-IPV/Hib.

Conclusion(s):

- In both groups only a small proportion (0.6%) of subjects reported rectal fever ≥ 40°C and no statistically significant difference was found between groups.
- No clinically relevant difference was observed between groups with respect to the different grades of fever analyzed, or with respect to the use of anti-pyretic medication.
- No convulsions were observed within 30 days following DTPa-HBV-IPV/Hib booster vaccination.
- The incidence of SAEs within 30 days post vaccination was similar between groups (< 1%).
- The number of large injection site reactions was similar between groups (2.5 to 2.1 %). Extensive swelling reactions (defined as swelling of the injected limb involving an adjacent joint) were similarly rare (0.1%) in both groups and in line with what has been previously reported.

Date of report: 11 June 2002

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** Infanrix™ hexa **Name of active substance:** Diphtheria and tetanus toxoids, PT, FHA, PRN, HBsAg, poliovirus types 1, 2, 3 and PRP.	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Title of the study: Open, multicentric, phase IV clinical trial to assess the immunogenicity and reactogenicity of GSK Biologicals' DTPa-HBV-IPV/Hib vaccine (Infanrix™ hexa) when given as a booster dose to children aged 11 to 23 months previously primed at 2, 4 and 6 months of age either with Aventis Pasteur's DTPa-HBV-IPV-Hib vaccine (Hexavac™) or GSK Biologicals' DTPa-HBV-IPV/Hib vaccine (Infanrix™ hexa) in study DTPa-HBV-IPV-086.

Principal Investigator: s22
The study was conducted by 38 investigators, all located in Germany.

Study Centres: This study was conducted in 38 centres in Germany.

Publication (reference): Not published as of March 2005

Study period: Study Initiation Date: 18 February 2003 Study Completion Date: 2 July 2003	**Clinical phase:** IV

Objectives:

Primary:

- To compare the immunogenicity of the hepatitis B and *Haemophilus influenzae* type B components of Infanrix™ hexa when given as a booster dose in the second year of life to children primed with GSK Biologicals' Infanrix ™ hexa vs. children primed with Aventis Pasteur's Hexavac™.

Secondary:

- Prior to the booster vaccination in the second year of life, to compare the persistence of antibodies against hepatitis B and *Haemophilus influenzae* type B, induced by a primary vaccination with GSK Biologicals' Infanrix™ hexa vs. Aventis Pasteur's Hexavac™.
- To assess the immunogenicity of the other components of Infanrix ™ hexa when given as a booster dose in the second year of life to children primed at 2, 4 and 6 months of age with either Aventis Pasteur's Hexavac™ or GSK Biologicals' Infanrix™ hexa.
- To assess the safety and reactogenicity of Infanrix™ hexa when given as a booster dose in the second year of life to children primed with 3 doses of either Infanrix™ hexa or Hexavac™.

Study design:
Open, multi-centric, non-randomized, self-contained study in Germany with the same two groups as in primary study. The subjects from the two groups in the primary study (Group primed with Hexavac™ and Group primed with Infanrix™ hexa) were administered a booster dose of Infanrix™ hexa in the second year of life. Two blood samples were taken, one before the booster dose and the other, one month after the booster dose.

Number of subjects:
Planned: 374 (187 in each group)
Enrolled: 330 (164 in the Hexavac™ primed group and 166 in the Infanrix™ hexa primed group)
Completed: 326 (163 in the Hexavac™ primed group and 163 in the Infanrix™ hexa primed group)
Safety: Total vaccinated cohort: 329 (163 in the Hexavac™ primed group and 166 in the Infanrix™ hexa primed group)
Immunogenicity: According-to-protocol (ATP) Cohort: 313 (155 in the Hexavac™ primed group and 158 in the Infanrix™ hexa primed group)
There were no drop-outs due to SAEs.

Doc ID 1 1

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** Infanrix™ hexa **Name of active substance:** Diphtheria and tetanus toxoids, PT, FHA, PRN, HBsAg, poliovirus types 1, 2, 3 and PRP.	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Diagnosis and criteria for inclusion:
A male or female between 11 and 23 months of age at the time of booster vaccination, who had completed the full three-dose primary vaccination course with either Infanrix™ hexa or Hexavac™ in study DTPa-HBV-IPV-086. All subjects were free of obvious health problems as established by medical history and clinical examination before entering into the study, and written informed consent was obtained from the parent or guardian before study entry.

Study vaccine, dose, mode of administration, lot no.:
Vaccination schedule/site: All subjects received a single dose of Infanrix ™ hexa (DTPa-HBV-IPV/Hib) intramuscularly in the right anterolateral thigh.
Vaccine composition/ dose/ lot number: After reconstitution of the lyophilised Hib component (Lot No.: Hib429A47) using the liquid DTPa-HBV-IPV component (Lot No.: 21892C9), one dose (0.5 ml) of GSK Biologicals' DTPa-HBV-IPV/Hib (Lot No: 21H0097) vaccine contained: ≥ 30 IU of diphtheria toxoid, ≥ 40 IU of tetanus toxoid, three acellular pertussis antigens: 25 µg of pertussis toxoid (PT), 25 µg of filamentous haemagglutinin (FHA) and 8 µg of pertactin (PRN), 10 µg of recombinant hepatitis B surface antigen (HBsAg), 40 D antigen units of poliovirus type 1, 8 D antigen units of poliovirus type 2, 32 D antigen units of poliovirus type 3, 10 µg of polyribosyl-ribitol phosphate (PRP), conjugated to 20-40 µg of tetanus toxoid, 0.82 mg of aluminium as salts, 12.6 mg of lactose, ≤ 2.5 mg of 2-phenoxyethanol, 150 mM of Sodium chloride, ≤ 100 µg of formalin, ≤ 25 µg of neomycin sulphate and ≤ 50 µg of Polysorbate.

Duration of treatment: The duration of study was approximately one month for each subject.

Criteria for evaluation:
Immunogenicity: Measurement of concentrations/ titres of antibodies against all vaccine antigens (HBsAg, PRP, diphtheria and tetanus toxoids, PT, FHA, PRN, poliovirus types 1, 2 and 3) at both blood sampling time points.
Safety: Recording of solicited local and general symptoms by the parents/ guardians during the 4-day (Day 0-Day 3) follow-up period after each dose. Recording of unsolicited symptoms and Serious Adverse Events (SAEs) occurring during the 31-day follow-up period (Day 0- Day 30) after the booster dose.

Statistical methods:
Demography: Demographic characteristics (mean age in months with standard deviation, gender, race) of the total vaccinated cohort and ATP immunogenicity cohort were tabulated.
Immunogenicity: Analysis (for both booster response and antibody persistence) was performed only on the ATP immunogenicity cohort. For each antibody and time point, seropositivity/seroprotection rates and their exact 95% confidence interval (CI), GMTs/GMCs and their 95% CI were tabulated; Booster vaccine response rates to pertussis antigens, with exact 95% CIs, were calculated. GMTs/GMCs calculations were performed taking the anti-log of the mean of the log titre transformations. Antibody titres below the cut-off of the assay were given an arbitrary value of half the cut-off for the purpose of GMT/GMC calculation. Pre and post-booster antibody concentrations/titres distributions were investigated using Reverse Cumulative Curves (RCCs).
The immunogenicity of the Infanrix™ hexa vaccine was compared with that of Hexavac™ vaccines by computing both the 95% CI for the group GMC/GMT ratio and the standardized asymptotic 95% CI for the difference in seroprotection/vaccine response rates for each antigen at each timepoint. The fact that 95% CI on the GMC/GMT ratios excluded 1 or that the 95% CI on the differences in seroprotection/vaccine response rates excluded 0% was used to highlight possible differences between groups. Statistically significant findings should be interpreted with caution because the risk of error due to the multiplicity of comparisons was not taken into account.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** Infanrix™ hexa **Name of active substance:** Diphtheria and tetanus toxoids, PT, FHA, PRN, HBsAg, poliovirus types 1, 2, 3 and PRP.	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Finally in order to evaluate a potential bias caused by drop-outs after the primary study, a descriptive analysis of immunogenicity, one month post-primary was performed on the total primary cohort (all subjects enrolled in primary study), based on participation/non-participation in the booster study.
Safety: The primary analysis of safety and reactogenicity was based on the total vaccinated cohort. For each type of solicited symptom, any symptom, grade "3" symptoms and symptoms with causal relationship to vaccination, the percentage of subjects reporting a symptom and its exact 95% CI was tabulated by group. The percentages of subjects with unsolicited symptoms (any, grade "3" and with causal relationship to vaccination, separately) were tabulated with exact 95% CI by group and by WHO preferred term. SAEs were reported during the entire study period, extensive local reactions and discontinuations due to AEs were to be reported. The percentage of subjects reporting each solicited symptom was compared between the Hexavac™ primed group and Infanrix™ hexa primed group using the two-sided Fisher Exact test.

Summary:
Demography Results:
The demographic profiles of the two groups of subjects were comparable with respect to mean age, gender and racial distribution. The mean age of the total vaccinated cohort was 14.6 months with a standard deviation of 1.30. The male: female ratio was 1.25 and the majority of the study population was white (96%).
Immunogenicity Results:
Antibody persistence:

- Before booster vaccination, the percentage of subjects with anti-HBs antibody concentration ≥ 10 mIU/ml, with anti-PRP concentration ≥ 0.15 µg/ml and associated GMCs were statistically significantly higher in children primed with Infanrix™ hexa than in those primed with Hexavac™.
- Statistically significantly higher seropositivity/seroprotection rates were also observed for anti-PRN, and anti-poliovirus types 1 and 3 antibodies in the Infanrix™ hexa primed group. The GMCs/GMTs of anti-PRN and anti-poliovirus types 1, 2 and 3 antibodies were also statistically significantly higher in the Infanrix™ hexa primed group compared to the group primed with Hexavac™.

Booster response:

- One month after booster vaccination, a marked booster response to all vaccine antigens was observed in the two groups.
- The response to booster vaccination was similar in the two groups, with at least 98% of subjects in both groups reaching seroprotective antibody levels against hepatitis B, PRP, diphtheria, tetanus, and poliovirus types 1, 2 and 3. Vaccine response rates to pertussis, antigens ranged from 86.0% to 98.1% in the two groups.
- Statistically significantly higher antibody concentrations/titres to HBsAg, PRP and polio types 2 and 3 were observed in the Infanrix™ hexa primed group (95% CI on difference in GMC/GMT not including 1; corresponding to a p-value < 0.05).
- Statistically significantly higher anti-PRN antibody concentrations in the Infanrix™ hexa primed group and statistically significantly higher anti-FHA antibody concentrations in the Hexavac™ primed group were observed.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** Infanrix™ hexa **Name of active substance:** Diphtheria and tetanus toxoids, PT, FHA, PRN, HBsAg, poliovirus types 1, 2, 3 and PRP.	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Table 1: Seropositivity/seroprotection/vaccine response rates and GMC/GMT with 95% CI for antibodies against all vaccine antigens for the ATP immunogenicity cohort:

Antibodies	Timing	Hexavac™ primed Group					Infanrix™ hexa primed Group				
		N	SP (%)	GMC/ GMT	L.L.	U.L.	N	SP (%)	GMC/ GMT	L.L.	U.L.
Anti-PRP (≥ 0.15 µg/ml)	Pre	153	75.8	0.384	0.311	0.474	157	92.4	0.569	0.477	0.680
	Post	155	98.7	22.924	17.680	29.723	158	99.4	40.895	32.257	51.848
Anti-PRP (≥ 1 µg/ml)	Pre	153	22.2	-	-	-	157	25.5	-	-	-
	Post	155	94.8	-	-	-	158	96.8	-	-	-
Anti-HBs (≥ 10 mIU/ml)	Pre	152	79.6	39.8	31.5	50.2	157	96.8	196.0	156.0	246.3
	Post	154	98.1	3141.8	2334.1	4229.1	157	100.0	7517.3	5876.2	9616.7
Anti-diphtheria (≥ 0.1 IU/ml)	Pre	152	75.7	0.255	0.209	0.311	155	76.8	0.313	0.254	0.387
	Post	155	99.4	5.174	4.384	6.107	157	100.0	4.916	4.154	5.819
Anti-tetanus (≥ 0.1 IU/ml)	Pre	152	98.7	0.611	0.530	0.705	155	98.1	0.499	0.434	0.573
	Post	155	100.0	6.506	5.753	7.356	157	100.0	6.592	5.724	7.592
Anti-poliovirus type 1	Pre	143	79.0	34.3	26.5	44.5	142	88.7	80.8	61.8	105.5
	Post	139	100.0	1063.2	865.7	1305.7	144	100.0	1399.9	1155.4	1696.1
Anti-poliovirus type 2	Pre	142	83.1	33.3	26.2	42.3	144	86.8	72.8	54.9	96.5
	Post	140	99.3	1141.8	947.1	1376.5	143	100.0	1607.0	1307.5	1975.0
Anti-poliovirus type 3	Pre	141	87.2	49.4	38.3	63.7	144	95.8	238.2	182.9	310.2
	Post	134	99.3	1589.8	1231.2	2052.9	146	100.0	3230.5	2713.4	3846.3
		N	VR (%)	GMC	L.L.	U.L.	N	VR (%)	GMC	L.L.	U.L.
Anti-PT	Post	150	98.0	167.2	147.6	189.4	150	93.3	143.6	126.0	163.6
Anti-FHA	Post	151	94.7	566.0	502.5	637.4	157	86.0	383.7	339.6	433.4
Anti-PRN	Post	152	94.1	25.1	21.5	29.4	154	98.1	396.1	343.8	456.3

Pre: Blood sampling prior to booster vaccination; Post: Blood sampling one month after boostervaccination
N: Number of subjects with available results; GMC/GMT: Geometric mean concentration/titre
SP (%): Percentage of subjects reaching the specified cut-off
VR (%): Percentage of responders (i.e. subjects who showed a vaccine response)
Vaccine response for all pertussis antigens was defined as: Appearance of antibodies in subjects who were seronegative at the pre-vaccination time point (i.e. with concentrations < 5 El.U/ml) or at least 2-fold increase of pre-vaccination antibody concentrations in subjects who were seropositive at the pre-vaccination time point (i.e. with concentrations ≥ 5 El.U/ml).
L.L. and U.L.: lower and upper limit of exact 95% confidence interval
Bold text identifies endpoints for which a statistically significant group difference was observed ((95% CI on difference in GMC not including 1; corresponding to a p-value <0.05).

Safety Results: For the total vaccinated cohort:
Any symptom (solicited/ unsolicited): The subjects primed with Infanrix™ hexa tended to show a higher incidence of symptoms after the Infanrix™ hexa booster as compared to the subjects primed with Hexavac™.
Solicited local symptoms: The incidence of solicited local symptoms was higher in the Infanrix™ hexa primed group than in the Hexavac™ primed group. Redness was the most frequently reported solicited local symptom (with an incidence of 39.3% in the Hexavac™ primed group and of 57.8% in the Infanrix™ hexa primed group). The percentage of subjects with grade "3" redness was 4.9% in the Hexavac™ primed group and 9.0% in the Infanrix™ hexa primed group.
Solicited general symptoms: The incidence of solicited general symptoms regardless of intensity and of grade "3" solicited symptoms did not statistically significantly differ between the two groups.Irritability (40.5%) and drowsiness (39.2%) were the most frequently reported solicited general symptoms in the Hexavac™ primed group and in the Infanrix™ hexa primed group, respectively. The majority of solicited general symptoms reported in both groups were considered by the investigator to have a causal

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** Infanrix™ hexa **Name of active substance:** Diphtheria and tetanus toxoids, PT, FHA, PRN, HBsAg, poliovirus types 1, 2, 3 and PRP.	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

relationship to study vaccination. Fever >39.5°C was the most frequently reported grade "3" solicited general symptom in both groups (3.1% in the Hexavac™ primed group and 2.4% in the Infanrix™ hexa primed group). Grade "3" fever that was causally related to vaccination was reported for 1.8% of subjects in the Hexavac™ primed group and 2.4% in the Infanrix™ hexa primed group. The percentage of subjects with fever > 40°C was similar in the two groups (1.8% in Hexavac ™ primed group and 1.2% in Infanrix™ hexa primed group).

Unsolicited symptoms: The percentage of subjects with at least one unsolicited symptom during the 31-day follow-up period was 33.7% in the Hexavac™ primed group and 36.1% in the Infanrix™ hexa primed group. A total of 0.6% of subjects in Hexavac™ primed group and 1.8% of subjects in Infanrix™ hexa primed group reported unsolicited symptoms that were causally related to vaccination during the 31-day follow-up period after vaccination.

Large injection site reactions: Four subjects (all in the Infanrix™ hexa primed group) reported large injection site reactions. All of these reactions were either limited to the immedaite vicinity of the injection site or represented diffuse swelling that did not extend to an adjacent joint. All large injection site reactions resolved spontaneously without sequelae.

Serious Adverse Events: One subject (n° 71 in the Infanrix™ hexa primed group) reported an SAE (rotaviral infection leading to hospitalisation) three days after the booster. This event was not considered by the investigator to be causally related to vaccination.

Concomitant medication: A similar proportion of subjects in both groups (6.7% in Hexavac™ primed group and 6.6% in Infanrix™ hexa primed group) received antipyretics during the 4-day follow-up period after vaccination.

Table 2: Reactogenicity during the 4-day follow-up period (Days 0-3) after booster vaccination, for the total vaccinated cohort is presented in the following table:

Symptom	Intensity	Hexavac™ primed group (N = 163)				Infanrix™ hexa primed group (N = 166)			
		n	%	L.L.	U.L.	n	%	L.L.	U.L.
Any symptom (solicited/ unsolicited)		121	74.2	66.8	80.8	138	83.1	76.6	88.5
Any grade "3" symptom (solicited/ unsolicited)		20	12.3	7.7	18.3	29	17.5	12.0	24.1
Solicited local symptoms:									
Pain	Any	44	27.0	20.3	34.5	65	39.2	31.7	47.0
	Grade "3"	1	0.6	0.0	3.4	6	3.6	1.3	7.7
Redness	Any	64	39.3	31.7	47.2	96	57.8	49.9	65.4
	>20 mm	8	4.9	2.1	9.4	15	9.0	5.1	14.5
Swelling	Any	47	28.8	22.0	36.4	67	40.4	32.8	48.2
	>20mm	6	3.7	1.4	7.8	13	7.8	4.2	13.0
Solicited general symptoms:									
Drowsiness	Any	58	35.6	28.3	43.4	65	39.2	31.7	47.0
	Grade "3"	1	0.6	0.0	3.4	2	1.2	0.1	4.3
	Causally related	48	29.4	22.6	37.1	56	33.7	26.6	41.5
	Grade "3" Causally related	1	0.6	0.0	3.4	2	1.2	0.1	4.3
Irritability	Any	66	40.5	32.9	48.4	64	38.6	31.1	46.4
	Grade "3"	1	0.6	0.0	3.4	3	1.8	0.4	5.2
	Causally related	52	31.9	24.8	39.6	55	33.1	26.0	40.8
	Grade "3" Causally related	1	0.6	0.0	3.4	3	1.8	0.4	5.2

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium Name of Finished Product: Infanrix™ hexa Name of active substance: Diphtheria and tetanus toxoids, PT, FHA, PRN, HBsAg, poliovirus types 1, 2, 3 and PRP.	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

Symptom	Intensity	Hexavac™ primed group (N = 163)				Infanrix™ hexa primed group (N = 166)			
		n	%	L.L.	U.L.	n	%	L.L.	U.L.
Loss of Appetite	Any	38	23.3	17.1	30.6	50	30.1	23.3	37.7
	Grade "3"	1	0.6	0.0	3.4	1	0.6	0.0	3.3
	Causally related	26	16.0	10.7	22.5	41	24.7	18.3	32.0
	Grade "3" Causally related	1	0.6	0.0	3.4	1	0.6	0.0	3.3
Fever (rectal temperature)	Any	57	35.0	27.7	42.8	52	31.3	24.4	39.0
	Causally related	46	28.2	21.5	35.8	44	26.5	20.0	33.9
	> 39.5°C Causally related	3	1.8	0.4	5.3	4	2.4	0.7	6.1
	≥ 38.0°C	57	35.0	27.7	42.8	52	31.3	24.4	39.0
	> 38.5°C	17	10.4	6.2	16.2	17	10.2	6.1	15.9
	> 39.0°C	7	4.3	1.7	8.6	9	5.4	2.5	10.0
	> 39.5°C	5	3.1	1.0	7.0	4	2.4	0.7	6.1
	> 40.0°C	3	1.8	0.4	5.3	2	1.2	0.1	4.3

N: Number of subjects having received at least one dose
n (%): Number (percentage) of subjects reporting a specified symptom
Any: Any solicited symptom (irrespective of intensity grade or causality)
Grade "3" pain: Cried when limb was moved/ spontaneously painful; Grade "3" drowsiness: Drowsiness that prevented normal activity
Grade "3" irritability: Crying that could not be comforted/ prevented normal activity; Grade "3" loss of appetite: Not eating at all
Causally Related: Symptoms considered by the investigator to have a causal relationship to vaccination
L.L., U.L.: lower and upper limits of 95% confidence interval
Bold text identifies endpoints for which a statistically significant group difference was observed (Fisher exact p-value < 0.05)

Conclusions:

On the basis of the descriptive and exploratory inferential analyses, it can be concluded that:

- Primary vaccination with Infanrix™ hexa resulted in higher levels of antibodies to HBs, PRP and poliovirus types at the time of booster vaccination compared to primary vaccination with Hexavac™, both in terms of seroprotection rate and of GMCs/ GMTs.
- Booster vaccination with Infanrix™ hexa elicited strong immune responses to all vaccine antigens in subjects primed either with Infanrix™ hexa or Hexavac™. After booster vaccination, at least 98% of the subjects in both study groups were seroprotected against hepatitis B, diphtheria, tetanus, PRP and the three poliovirus types; at least 86% of the subjects mounted a vaccine response to the three pertussis antigens.
- Local symptoms after booster vaccination with Infanrix™ hexa were more frequently reported in subjects primed with Infanrix™ hexa than in subjects primed with Hexavac™. However the incidence of grade 3 local symptoms was not statistically significantly different between the two groups. The incidence of general symptoms was similar in the two groups, and few subjects reported fever >39.5°C.
- Few unsolicited symptoms were considered by the investigator to be related to vaccination. One subject in the Infanrix™ hexa primed group experienced an SAE (viral infection) that was not causally related to the vaccination by the investigator.

Date of report: March 2005

Document 1

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** **Name of active substance:** DTPa, HBV, IPV, *N. meningitidis* capsular polysaccharide C and *H. influenzae* protein D conjugate	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Title of the study : A phase II, open, randomized, controlled study to assess the immune memory induced by a primary vaccination course of GlaxoSmithKline Biologicals' (GSK Biologicals') DTPa-HBV-IPV extemporaneously mixed with GSK Biologicals' Hib-MenC by giving meningococcal AC polysaccharide, and the safety, reactogenicity and immunogenicity of a booster dose of GSK Biologicals' DTPa-HBV-IPV extemporaneously mixed with Hib-MenC toddlers primed in study 404286/001.

Principal Investigator: s22 [redacted]

Study Centre: Johannes-Gutenberg-Universität
Langenbeckstr. 1
55101 Mainz
Germany

Publication (reference): Not published as of October 22, 2003

Study period: **Clinical phase:** II
Date of first visit: November 03, 2000
Date of last visit: April 11, 2001 (end of active phase)

Objectives:

Primary objective

To evaluate the immune memory induced by primary vaccination with the DTPa-HBV-IPV/Hib-MenC combined vaccine by giving one fifth of a dose of Mencevax™ AC to healthy 12 to 24 month-old toddlers who were primed with one of the three formulations of GSK Biologicals' DTPa-HBV-IPV/Hib-MenC vaccine in infancy.

Secondary objectives

- Prior to the administration of a booster dose, to evaluate the persistence of the immune response induced by a primary vaccination course with one of three different formulations of GSK Biologicals' DTPa-HBV-IPV extemporaneously mixed with Hib-MenC.
- To evaluate the immune response induced by a booster dose of Hib-MenC extemporaneously mixed with DTPa-HBV-IPV in toddlers primed with one of the three formulations of GSK Biologicals' DTPa-HBV-IPV/Hib-MenC vaccine in infancy.
- Prior to the administration of a booster dose, to evaluate the long-term safety of a primary vaccination course with one of three different formulations of GSK Biologicals' DTPa-HBV-IPV extemporaneously mixed with Hib-MenC.
- To evaluate the safety and reactogenicity induced by a booster dose of DTPa-HBV-IPV/Hib-MenC combined vaccine in toddlers primed with one of three different formulations of GSK Biologicals' DTPa-HBV-IPV extemporaneously mixed with Hib-MenC.
- To evaluate the safety and reactogenicity induced by one fifth of a dose of Mencevax™ AC to healthy 12 to 24 month-old toddlers who were primed with one of the three formulations of GSK Biologicals' DTPa-HBV-IPV/Hib-MenC vaccine in infancy.

Document 1

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** **Name of active substance:** DTPa, HBV, IPV, *N. meningitidis* capsular polysaccharide C and *H. influenzae* protein D conjugate	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Methodology:
Study design: Phase II, open, randomized, booster study with four groups of toddlers between 12 and 24 months of age. The study was conducted in subjects having participated in the primary vaccination study 404286/001 which included the following four groups:
Group A: vaccinated with DTPa-HBV- IPV_{mod}/Hib-MenC
Group B: vaccinated with DTPa-HBV-IPV/Hib-$MenC_{ads}$
Group C: vaccinated with DTPa-HBV-IPV/Hib-MenC
Group D: vaccinated with DTPa-HBV-IPV/Hib

Those subjects who had received a DTPa-HBV-IPV/Hib-MenC vaccine in the primary study 404286/001 were randomized (1:2) to two groups (Groups W and X):

- Group W received a booster dose of DTPa-HBV-IPV/Hib and 1/5th dose of Mencevax™ AC as separate injections; it included sub-Groups WA, WB, WC according to the formulation received during the primary vaccination study.
- Group X received a booster dose of DTPa-HBV-IPV/Hib-MenC (classic formulation, Hib-MenC non_ads) as a single injection; it included sub-Groups XA, XB, XC according to the formulation received during the primary vaccination study.

Those subjects who had received the DTPa-HBV-IPV/Hib vaccine (control) in the primary study 404286/001 were randomized (1:1) to two control groups (Groups Y and Z):

- Group Y received a booster dose of DTPa-HBV-IPV/Hib and 1/5th dose of Mencevax™ AC as separate injections.
- Group Z received a booster dose of DTPa-HBV-IPV/Hib as a single injection.

Two blood samples (3.5 ml) for serology were taken, one pre-vaccination, the other either 7 days post-vaccination (Groups W, Y) or one month post-vaccination (Groups X and Z).
The study was conducted at several sites in Germany, data collection was done using electronic Case Report Forms (eCRF).

Number of subjects:
Planned: 413 subjects were planned to be enrolled in order to have 368 evaluable subjects; *Enrolled*: 385 (96, 194, 49, and 46 in Groups W, X, Y and Z); *Completed* to Day 30 after vaccination (end of active phase): 382; *Drop-out*: 3, none due to serious adverse events.
Total cohort (analysed safety cohort): 385.
ATP immunogenicity cohort (primary cohort for immune memory and vaccine response immunogenicity analysis): 340.
ATP safety cohort (primary cohort for persistence immunogenicity analysis): 354.

Diagnosis and criteria for inclusion:
Healthy male or female infants, 12 to 24 months of age, having participated at the study 404286/001.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** **Name of active substance:** DTPa, HBV, IPV, *N. meningitidis* capsular polysaccharide C and *H. influenzae* protein D conjugate	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Test product, dose, mode of administration, lot No.:

Test product	Formulation (contents per dose)	Route	Schedule	Lot
Mencevax ™ AC	Purified polysaccharides from *N. meningitidis* of serogroup A and C (content per dose, each: 50 µg; note: only 1/5th dose was administered)	IM/ left thigh	1/5th dose at 1st visit (Groups W and Y)	N288A41/ D
Hib-MenC	Conjugate of *H. influenzae* type b and tetanus toxoid; conjugate of *N. meningitidis* C capsular polysaccharide and *H. influenzae* protein D; polyribosyl-ribitol-phosphate: 10 µg, tetanus toxoid: 20-40 µg, polysaccharide C: 10 µg, protein D: 110 µg	IM/ right thigh	1 dose at 1st visit (Group X)	DCH004A 48
DTPa-HBV-IPV#	Diphtheria, tetanus, acellular pertussis, hepatitis B and polio vaccine: diphtheria toxoid: ≥ 30 IU, tetanus toxoid ≥ 40 IU, pertussis toxin: 25 µg, FHA: 25 µg, PRN: 8 µg, HBs: 10 µg, poliovirus type 1: 40 D antigen units, poliovirus type 2: 8 D antigen units, poliovirus type 3: 32 D antigen units, phenoxyethanol: ≤ 2.5 mg, aluminium: 0.7 mg	IM/ right thigh	1 dose at 1st visit (all groups)	21833A9
Hib# (control vaccine)	Conjugate of *H. influenzae* type b and tetanus toxoid vaccine: polyribosyl-ribitol-phosphate: 10 µg, tetanus toxoid: 20-40 µg, aluminium: 0.12 mg	IM/ right thigh	1 dose at 1st visit (Groups W, Y, Z)	Hib273A4 7/M

Dose: one dose of the lyophilized vaccines Hib-MenC (Group X) or Hib (Group W, Y, Z) was reconstituted with one dose (0.5 ml) of the DTPa-HBV-IPV vaccine. One dose of the lyophilized Mencevax™ AC was reconstituted with 1.0 ml diluent, supplied in two separate vials/ampoules (each containing 0.5 ml of diluent, lot number: 99K17/22C/M), and 1/5th of it was administered as separate injection to Groups W and Y.

Duration of study for each subject: Approximately 30 days for the active phase and 6 months for the long-term safety follow-up.

Criteria for evaluation:
Immunogenicity:
Primary End point:
Seven (7) days after booster vaccination: Determination of bactericidal antibody titres against meningococcal C (SBA-MenC) by a bactericidal test, and determination of antibody concentrations to meningococcal C polysaccharide (anti-PSC) by ELISA (for Groups W and Y).

in the meantime, DTPa-HBV-IPV / Hib is licensed under the tradename Infanrix®Hexa

Document 1

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** **Name of active substance:** DTPa, HBV, IPV, *N. meningitidis* capsular polysaccharide C and *H. influenzae* protein D conjugate	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Secondary Endpoints:

Prior to and 30 days after booster vaccination: Determination of bactericidal antibody titres against meningococcal C (SBA-MenC) by a bactericidal test, and determination of antibody concentrations to meningococcal C polysaccharide (anti-PSC) by ELISA. Determination of antibody concentrations/titres for protein D (PD), polyribosyl-ribitol-phospbate (PRP), diphtheria toxoid (D), tetanus toxoid (T), pertussis toxoid (PT), pertactin (PRN) and filamentous haemagglutin (FHA) by ELISA. Antibodies against polio virus type 1, 2, and 3 were determined by a virus micro-neutralisation test, and antibodies to the hepatitis B surface antigen (HBs) were measured using a commercially available kit (ELISA).

Safety:

- 8-day (Day 0 to Day 7) follow-up after administration of booster dose for grade 3 solicited symptoms as well as for each solicited adverse event.
- 31-day (Day 0 to Day 30) follow-up after administration of booster dose for unsolicited non-serious adverse events as well as for any serious adverse event.

Serious adverse events were recorded from the end of the primary study (404286/001) during the entire study period until 6 months after the booster dose administration.

Statistical methods:

- Determination of mean age (with range and standard deviation), and racial and gender composition.

Two analyses of immunogenicity were performed based on the ATP cohort for immunogenicity (for analyses of immune memory and booster response) or the ATP cohort for safety (for analysis of peristence), and based on the Total cohort. These included:

Evaluation of immune memory (before and 7 days after Mencevax™ AC administration) for subjects primed with different DTPa-HBV-IPV/Hib-MenC formulations (Group W and sub-Groups WA, WB, WC, control Group Y).

- Determination of geometric mean concentrations/titres (GMCs/GMTs) with 95% CI for MenC antigens
- Determination of seropositivity rates with exact 95% CI for SBA-MenC and anti-PSC
- Investigation of antibody concentrations/titres after Mencevax™ AC administration by using reverse cumulative curves for each antigen
- Determination of the 95% CI for the post-vaccination GMCs and GMTs ratio between each group and Group Y using an ANOVA model

Evaluation of persistence (one month after priming and before booster vaccination) for subjects primed with the DTPa-HBV-IPV/Hib-MenC formulations (Group A; Group B, Group C, control Group D of the primary vaccination study 404211/001) and *Evaluation of the booster immune response* following the booster dose of DTPa-HBV-IPV/Hib-MenC (before and 30-days after booster vaccination) for subjects boosted with DTPa-HBV-IPV/Hib-MenC and primed with different DTPa-HBV-IPV/Hib-MenC formulations (Group X and sub-Groups XA, XB, XC, control Group Z):

- Tabulation of GMCs/GMTs with 95% CI for each treatment group and each antigen
- Calculation of seropositivity/seroprotection rates with exact 95% CI
- Investigation of antibody concentrations/titres using reverse cumulative curves

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium Name of Finished Product: Name of active substance: DTPa, HBV, IPV, *N. meningitidis* capsular polysaccharide C and *H. influenzae* protein D conjugate	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

Two analyses of *safety* were performed based on the ATP and Total cohort. These included:

- Tabulation of any adverse events with exact 95% CI, of at least one local adverse event and of at least one general adverse event reported during the follow-up period (Day 0 to 7 / Day 0 to 30 for solicited / unsolicited AEs, respectively) by group (and sub-Groups XA, XB, XC); tabulation of AEs rated as grade-3 (with a reasonable possibility that the vaccine contributed to the AE) with the exact 95% CI; tabulation of extensive swelling with the exact 95% CI per group; tabulation of the number and percentage with the exact 95% CI of subjects reporting unsolicited symptoms classified by WHO body system/WHO preferred term within 31 days after vaccination (Day 0 to 30); tabulation of the number of subjects who started to receive at least one type of medication after vaccination; description of all serious adverse events (SAE) during the study period up to 30 days after study drug administration. SAEs that were reported since the end of the primary study (404286/001) and SAEs that were reported during the long-term safety follow-up SAEs (up to 6 months after study drug administration) were also described.

SUMMARY-CONCLUSIONS :

Immunogenicity Results:

The evaluation of immune memory and the booster immune response was based on the ATP cohort for immunogenicity, the evaluation of persistence was based on the ATP cohort for safety (which was identical to the ATP cohort for persistence).

Immune memory (ATP cohort for immunogenicity); Groups W, Y; sub-Groups WA, WB, WC:

Seven days following the administration of the plain polysaccharide AC to Groups W and Y, 98.6 % and 94.4% of the subjects primed with the DTPa-HBV-IPV/Hib-MenC vaccines had SBA-MenC titres ≥ 1:8 and 1:128, respectively, whereas in the control Group Y 83.9 % of the subjects had SBA-MenC titres ≥ 1:8 and 1:128.

For both SBA-MenC and anti-PSC, the lower limits of the 95% CI of the GMT/C ratio (Group W and sub-Groups WA, WB, WC/ Group Y) were well above 1, indicating a higher immune response in Group W (and each sub-Group WA,WB, WC) versus Group Y and suggesting that immune memory was induced by primary vaccination with the DTPa-HBV-IPV/Hib-MenC formulations.

The subjects primed with the DTPa-HBV-IPV/Hib-MenC$_{sds}$ (sub-Group WB) tended to have a higher SBA-MenC GMT after the administration of the plain polysaccharide.

The GMTs and GMCs for anti-SBA-MenC and anti-PSC antibodies and the ratio of GMTs/Cs between Group W, sub-Groups WA, WB, WC versus the control Group Y are presented in Synopsis Table 1.

Document 1

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium Name of Finished Product: Name of active substance: DTPa, HBV, IPV, *N. meningitidis* capsular polysaccharide C and *H. influenzae* protein D conjugate	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

Synopsis Table 1: SBA-MenC and anti-PSC antibodies 7 days after booster vaccination: GMT/C and ratio between groups (ATP cohort for immunogenicity)

Antibody	(sub-) Group	N	GMT or GMC	Group ratio and 95% CI			
				ratio (sub-) Groups	Value	95%CI LL	UL
SBA-MenC	W	72	886.3	W vs Y	4.84	2.46	9.51
	WA	25	776.0	WA vs Y	4.24	1.77	10.16
	WB	26	1336.8	WB vs Y	7.30	3.12	17.10
	WC	21	624.1	WC vs Y	3.41	1.27	9.17
	Y	31	183.1				
anti-PSC	W	79	9.73	W vs Y	4.71	3.18	6.97
	WA	26	10.56	WA vs Y	5.11	2.87	9.11
	WB	28	9.85	WB vs Y	4.77	2.82	8.07
	WC	25	8.81	WC vs Y	4.26	2.38	7.64
	Y	42	2.07				

sub-Group WA: subjects primed with DTPa-HBV-IPV$_{mod}$/Hib-MenC and boosted with DTPa-HBV-IPV/Hib+1/5 dose of Mencevax™ AC

sub-Group WB: subjects primed with DTPa-HBV-IPV/Hib-MenC$_{ads}$ and boosted with DTPa-HBV-IPV/Hib+1/5 dose of Mencevax™ AC

sub-Group WC: subjects primed with DTPa-HBV-IPV/Hib-MenC and boosted with DTPa-HBV-IPV/Hib+1/5 dose of Mencevax™ AC

Group W: sum of subjects in sub-Groups WA, WB and WC

Group Y: subjects primed with DTPa-HBV-IPV/Hib and boosted with DTPa-HBV-IPV/Hib+1/5 dose of Mencevax™ AC

N = number of subjects with available results; GMT / C / R = Geometric mean titre / concentration / ratio
95% CI = 95% confidence interval; LL = Lower Limit; UL = Upper Limit

Persistence (ATP cohort for safety); Groups A, B, C, D (primary vaccination course), pre-booster timepoint

- Anti-PRP: the percentage of subjects with anti-PRP ≥0.15 µg/ml was similar between Groups A, C (94.3%, 85.5%) and control Group D (92.9%), but tended to be lower in Group B (79.3 %).
- SBA-MenC and anti-PSC: 44.6-53.2% of the subjects of Groups A, B and C had SBA-MenC ≥ 1:8 versus 7.0% in the control Group D. There were no differences between the three vaccine formulations. 81.6-91.6% of the subjects had anti-PSC antibodies ≥ 0.3 µg/ml versus 2.4% in the control Group D (95% CIs non-overlapping).
- Protein D: 93.1-100% of the subjects of Groups A, B and C had anti-PD antibodies ≥100 EL.U/ml, versus 39.0% in the control group D.
- Pertussis: Most subjects had antibodies ≥5 EL.U/ml against PT, FHA and PRN; Group C had slightly lower anti-PRN, anti-PT and anti-FHA GMCs than the control Group D (non-overlapping 95% CI) and Group A had a lower anti-PRN GMC than the control Group D.
- Polio 1,2 and 3, hepatitis B, diphtheria and tetanus: the percentage of subjects above the respective seroprotective cut-off was similar between Groups A, B, C and control Group D (95% CI overlapping) with the exception of Group C for diphtheria (36.6% ≥0.1 IU/ml versus 61.0% in control Group D, 95% CI non-overlapping). Slight differences were noted for certain antibodies in terms of GMC/Ts.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium Name of Finished Product: Name of active substance: DTPa, HBV, IPV, *N. meningitidis* capsular polysaccharide C and *H. influenzae* protein D conjugate	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

Booster immune response (ATP cohort for immunogenicity); Groups X and Z; sub-Groups XA, XB, XC, one months post booster dose:

- Anti-PRP: the booster response was high in all groups; 98.2-100.0 % of the subjects in the sub-Groups XA, XB and XC and 97.4% of subjects in Group Z had anti-PRP ≥ 1.0 µg/ml, and GMCs were similar between groups.
- SBA-MenC and anti-PSC: the booster vaccine induced a high SBA-MenC booster response with a more than 30-fold GMT increase from the pre- to the post-booster timepoint in Group X; 93.2-100% of subjects in sub-Groups XA, XB and XC had SBA-MenC ≥ 1:8; sub-Group XA tended to have a lower GMT than the two other groups (465.8 vs 1024.0 and 935.5 for sub-Groups XB and XC, respectively). A 9-fold GMC increase from the pre- to the post-booster timepoint was observed for anti-PSC with GMCs being similar between sub-Groups XA, XB and XC.
- Protein D: the booster response was high (approximately 4-fold GMC increase) in all 3 sub-Groups XA, XB and XC, with no major difference between groups.
- Pertussis: the booster response of Group X (and each sub-Group) was high for PT, FHA and PRN with the GMCs post booster similar to the control Group Z.
- Polio 1,2 and 3, hepatitis B, diphtheria and tetanus: the booster vaccines induce a high immune response for each antigen; there were no differences between Group X (and sub-Groups Xa, XB and XC) and the control Group Z in terms of seroprotection; however, slight differences (non-overlapping 95% CI) were noted in terms if GMC/Ts for certain antigens in each sub-Group XA, XB, XC and for anti-Diphtheria between Group X and control Group Z.

Safety Results:

Safety evaluation was based on the Total cohort.

Synopsis Table 2 presents the incidence and nature of symptoms and grade 3 related symptoms reported within 31 days after booster vaccination, Synopsis Table 3 presents the incidence of fever and grade 3 related fever within 8 days post booster vaccination.

Synopsis Table 2: Incidence and nature of symptoms and grade 3 related symptoms (solicited and unsolicited) reported within 31 days after booster vaccination (Total cohort)

		Any symptom (%)		General symptom (%)		Local symptom (%)	
Group	N	Overall	Grade 3 rel.	Overall	Grade 3 rel.	Overall	Grade 3 rel.
Group W	96	83.3	13.5	79.2	4.2	61.5	9.4
Group X	191	81.7	15.2	73.3	3.1	52.9	12.6
Group Y	49	87.8	12.2	79.6	0.0	65.3	12.2
Group Z	46	76.1	6.5	69.6	0.0	45.7	6.5

Synopsis Table 3: Incidence of fever and Grade 3 related fever reported within 8 days after booster vaccination (Total cohort)

Group	N	Any fever (%)	>39°C (%)	>40°C (%)	>40°C and related (%)
W	96	46.9	11.5	1.0	1.0
X	191	41.9	10.5	1.6	1.6
Y	49	49.0	8.2	2.0	0.0
Z	46	56.5	15.2	0.0	0.0

Synopsis of study report 404286/006 (Hepta-006) page 7

Document 1

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium Name of Finished Product: Name of active substance: DTPa, HBV, IPV, *N. meningitidis* capsular polysaccharide C and *H. influenzae* protein D conjugate	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

Notes to Synopsis Table 2
N = number of symptom sheets completed; rel = related
Group W : subjects boosted with DTPa-HBV-IPV/Hib+1/5 dose of Mencevax™ AC
Group X : subjects boosted with DTPa-HBV-IPV/Hib-MenC
Group Y : subjects boosted with DTPa-HBV-IPV/Hib+1/5 dose of Mencevax™ AC
Group Z : subjects boosted with DTPa-HBV-IPV/Hib

Overall, the booster vaccines were well tolerated and there were no major differences between groups. The lowest incidence of local and general symptoms was observed for the control group (Group Z, subjects boosted with DTPa-HBV-IPV/Hib). The incidence of grade 3 symptoms assessed as probably or suspected to be related to vaccination ranged from 6.5 to 15.2%.

Redness was the most often reported solicited local symptom (34.8-56.3% of the subjects) and the DTPa-HBV-IPV/Hib-MenC booster (Group X) tended to induce a higher incidence of redness > 30 mm (8.9%) versus the DTPa-HBV-IPV/Hib booster (Group Z, 2.2 %). Overall, local grade 3 symptoms were reported by less than 9% of the subjects in each group, most of them resolved within the 8-day follow-up period. 11 subjects reported extensive swelling reactions. All but one incidence of these extensive swellings (diffuse swelling, not involving adjacent joint), were swellings > 50 mm around injection site, but not involving adjacent joints.

Fever (rectal temperature ≥ 38.0°C) was the most frequently reported solicited general symptom (41.9-56.5% of the subjects); in Groups W, X and Y fewer subjects had fever > 39°C (8.2-11.5%) than in the control Group Z (15.2%), but this was not statistically significant. The highest percentage of subjects with fever > 40°C was 2.0% (Group Y).

The percentage of subjects who experienced at least one unsolicited symptom was similar in all groups (range: 28.3 to 36.6%), the most frequently reported unsolicited symptom was upper respiratory tract infection (URTI) or bronchitis. Unsolicited Grade 3 symptoms (URTI and fever) were reported by one subject 15 days after vaccination with DTPa-HBV-IPV/Hib + 1/5 dose of Mencevax™ AC (Group Y): these adverse events were assessed by the investigator as not related to vaccination, the subject recovered without sequelae.

Serious adverse events (SAEs)

Long-term safety follow-up of primary vaccination course
A total of 32 SAEs were reported retrospectively for subjects who participated in the primary vaccination study (404286/001, time period: between 30 days after primary vaccination study and study start of the booster vaccination study). All these SAEs were assessed by the investigator as not related to vaccination. Most of the SAEs (27 out of 32) resolved without sequelae (one was fatal: drowning; one resolved with sequelae: scald; three were reported as unresolved at the time of closure of the report).

Within 30 days post booster vaccination
SAEs were reported by two subjects in Groups W and X (boosted with DTPa-HBV-IPV/Hib and DTPa-HBV-IPV/Hib-MenC, respectively). One of the two SAEs, anemia, was assessed as probably related to DTPa-HBV-IPV/Hib vaccination.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium Name of Finished Product: Name of active substance: DTPa, HBV, IPV, *N. meningitidis* capsular polysaccharide C and *H. influenzae* protein D conjugate	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

Long-term safety follow-up of booster vaccination course

A total of 10 subjects experienced SAEs during the long-term follow-up period (time period: between 30 days to 6 months post booster vaccination) of the booster vaccination course. All these adverse events were assessed by the investigator as not related to vaccination and resolved without sequelae.

Conclusions:

- The three different DTPa-HBV-IPV/Hib-MenC formulations given as three-dose primary vaccination to infants in their 3rd, 4th and 5th month of age (study 404286/001) induced immune memory. This was shown by the higher meningococcal immune response after administration of 10 µg meningococcal plain polysaccharide C in the second year of life compared to children who had not received a meningococcal serogroup C conjugate vaccine in infancy. Subjects in sub-Group WB, primed with the DTPa-HBV-IPV/Hib-MenC$_{ads}$, tended to have a higher SBA-MenC GMT.
- Overall the persistence of antibodies was good: the percentage of subjects with anti-PRP " 0.15 µg/ml was high in most groups, but tended to be lower in subjects primed with DTPa-HBV-IPV/Hib-MenCads (Group B); approximately half of the subjects bad bactericidal antibody titres " 1:8, in the same range as published data on meningococcal serogroup C vaccines[1,2]. The persistence of the immune response to the other antigens was similar between groups, except for the DTPa-HBV-IPV/Hib-MenC formulation that had lower GMCs for all pertussis antibodies and a lower % of subjects with protective levels of anti-diphtheria antibodies.
- A booster dose of DTPa-HBV-IPV/Hib-MenC given to children in their second year of life induced a high immune response for all antigens, and, for all common antigens, it was similar to the control group DTPa-HBV-IPV/Hib. The booster effect on the meningococcal serogroup C immunune response was high with 97.1% of the subjects (sub-Groups: 93.2– 100.0%) having bactericidal titres of at least 1:8. The GMTs of subjects primed with DTPa-HBV-IPVmod/Hib-MenC were slightly lower.
- The long-term safety follow-up of the primary vaccination course showed that the 3-dose primary vaccination schedule was well tolerated.
- The booster doses were well tolerated. Adding MenC-PD to the booster vaccination did not increase reactogenicity. More specifically, the incidence of fever and of extensive swelling was not increased in the groups that received a booster dose of DTPa-HBV-IPV/Hib-MenC. The incidence rate of high grade fever (> 40°C) should be carefully evaluated in further studies.

Date of report: October 22, 2003

[1] Richmond P, Borrow R, Miller E, et al. Meningococcal Serogroup C Conjugate Vaccine Is Immunogenic in Infancy and Primes for Memory. JID 1999, 199:1569-72

[2] Richmood P, Borrow R, Findlow J, et al. Evaluation of De-O-acetylated meningococcal C polysaccharide-tetanus toxoid conjugate vaccine in infancy: reactogenicity, immunogenicity, immunologic priming, and bactericidal activity against ●-acetylated and De-O-acetylated serogroup C strains. Infect Immun 2001 69(4):2378-82.

Document 1

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** **Name of Active Substance:** Diphtheria and tetanus toxoids, PRP, PT, PRN, FHA, poliovirus types 1, 2, 3, HAV, polysaccharide C-protein D conjugate	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Title of the study : 455697/001 (DTPa-HAV-IPV-001)
Open, randomized, multicentric, phase II clinical trial to assess the immunogenicity and reactogenicity of GSK Biologicals' DTPa-HAV-IPV and Hib-MenC vaccines when mixed extemporaneously and administered as a single booster dose to healthy children, 17 to 20 months of age, previously vaccinated with three doses of GSK Biologicals' DTPa-IPV/Hib vaccines in the DTPa-IPV-039 primary vaccination study.

Principal Investigator: s22 and s22

Study Centers: This study was conducted in 7 centers in Lithuania.

Publication (reference): Not published as of 23 July 2002.

Study period: Date of first visit: 4 January 2000
Date of last visit: 23 November 2000

Clinical phase: II

Objectives:
Primary:
- To assess the reactogenicity of the study vaccines in terms of Grade 3 local or general, solicited or unsolicited symptoms occurring within 8 days after vaccination, including any occurrence of extensive limb swelling.

Secondary:
- Safety and reactogenicity of the study vaccines in terms of occurrence of solicited and unsolicited symptoms and serious adverse events (SAEs).
- Immunogenicity of study vaccines in terms of antibody titres/concentration against all vaccine antigens one month after the first vaccine dose and anti-HAV antibody titres one month after each HAV dose.

Note: an analysis of persistence following the primary vaccination in DTPa-IPV/Hib can be found in the DTPa-IPV-043 study report.

Methodology:
Study design: Open, randomized, multicentric (seven centers) study with three parallel groups with a balanced allocation (1:1:1).
Group 1: DTPa-HAV-IPV vaccine mixed with Hib-MenC vaccine (DTPa-HAV-IPV/Hib-MenC) and a second dose of HAV 6 months later.
Group 2: DTPa-HAV-IPV vaccine mixed with Hib vaccine (DTPa-HAV-IPV/Hib) and a second dose of HAV 6 months later.
Group 3: DTPa-IPV vaccine mixed with Hib and concomitantly administered with HAV vaccine (DTPa-IPV/Hib + HAV) and a second dose of HAV 6 months later.
Note: Although vaccination in this study with DTPa, IPV and Hib are booster doses (subjects primed in study DTPa-IPV-039), the term "dose 1" will be used in this study report to refer to the booster dose of those vaccines and for the first dose of MenC and HAV.

Number of subjects:
Planned: 510 (170 per group)
Enrolled: 494 (Group 1= 166; Group 2 = 165; Group 3 = 163)
Completed: 479 (Group 1= 160; Group 2 = 161; Group 3 = 158)
Analysed according-to-protocol (ATP) for safety : 489 (Group 1 = 165; Group 2 = 163; Group 3 = 161)
Analysed for immunogenicity (ATP): 473 (Group 1 = 160; Group 2 = 156; Group 3 = 157)

DocID 1

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** **Name of Active Substance:** Diphtheria and tetanus toxoids, PRP, PT, PRN, FHA, poliovirus types 1, 2, 3, HAV, polysaccharide C-protein D conjugate	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Diagnosis and criteria for inclusion:
Healthy male or female toddlers between 17 and 20 months of age who had completed the primary vaccination course with DTPa-IPV/Hib vaccine in study 213503/039 (DTPa-IPV-039) were enrolled in this booster study. Written informed consent was obtained from the parent/guardian of the subjects.

Test product, dose, mode of administration, lot no.:
Vaccination schedule/site:
Group 1 received DTPa-HAV-IPV/Hib-MenC vaccine administered intramuscularly (IM) in the right thigh followed by a second dose of HAV vaccine 6 months later IM in the left thigh.
Group 2 received DTPa-HAV-IPV/Hib vaccine administered IM in the right thigh followed by a second dose of HAV vaccine 6 months later IM in the left thigh.
Vaccine/composition/dose/lot number:
GSK Biologicals' combined diphtheria, tetanus, acellular pertussis, hepatitis A, inactivated poliovirus (DTPa-HAV-IPV) vaccine containing per 0.5 ml dose: 25 mcg pertussis toxoid (PT), 25 mcg filamentous hemagglutinin (FHA), 8 mcg pertactin (PRN), ≥ 30 IU (25 Lf) diphtheria toxoid, ≥ 40 IU (10 Lf) tetanus toxoid, 40 D antigen units poliovirus type 1 (Mahoney strain), 8 D antigen units poliovirus type 2 (MEF-1 strain), 32 D antigen units poliovirus type 3 (Saukett strain), 720 ELISA Unit (EL.U) hepatitis A virus (HAV) (strain HM 175), ≤ 2.5 mg phenoxyethanol and 0.5 mg aluminium as salt. Lot no. D26701A2
GSK Biologicals' combined *Haemophilus influenzae type b* (Hib) - Meningococcal C (MenC) vaccine containing per 0.5 ml dose: 10 mcg polyribosyl ribitol phosphate (PRP) conjugated to 20-40 mcg tetanus toxoid, 10 mcg polysaccharide C (PSC) conjugated to 10 mcg protein D and 12.6 mg sucrose. Lot no. DCH002A46.
GSK Biologicals' *Haemophilus influenzae* type b (Hib) conjugate vaccine (*Hiberix*™) containing per 0.5 ml dose (after reconstitution): 10 mcg PRP, 20-40 mcg tetanus toxoid and 10 mg lactose. Lot no. HIB254A47
GSK Biologicals' hepatitis A vaccine (*Havrix*™) containing per 0.5 ml dose: 720 EL.U HAV (strain HM 175) and 0.25 mg aluminium. Lot no. VHA588C9/M.

Reference therapy, dose and mode of administration, batch number:
Vaccination schedule/site:
Group 3 received DTPa-IPV/Hib vaccine administered IM in the right thigh and HAV vaccine administered IM in the left thigh followed by a second dose of HAV vaccine 6 months later IM in the left thigh.
Vaccine/composition/dose/lot number:
GSK Biologicals' combined diphtheria, tetanus, acellular pertussis, inactivated polio (DTPa-IPV) vaccine containing per 0.5 ml dose: 25 mcg PT, 25 mcg FHA, 8 mcg PRN, ≥ 30 IU (25 Lf) diphtheria toxoid, ≥ 40 IU (10 Lf) tetanus toxoid, 40 D antigen units poliovirus type 1 (Mahoney strain), 8 D antigen units poliovirus type 2 (MEF strain), 32 D antigen units poliovirus type 3 (Saukett strain), ≤ 2.5 mg phenoxyethanol and 0.5 mg aluminium as salt. Lot no. D20751A2
The *Hiberix*™ vaccine and *Havrix*™ vaccine used were of the same composition and lot no. as described above.

Duration of treatment: Approximately 7 months per subject.

Document 1

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** **Name of Active Substance:** Diphtheria and tetanus toxoids, PRP, PT, PRN, FHA, poliovirus types 1, 2, 3, HAV, polysaccharide C-protein D conjugate	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Criteria for evaluation:

Safety/reactogenicity:

Solicited local (pain, redness, and swelling) and general (drowsiness, fever, irritability/fussiness and loss of appetite) symptoms were assessed by the parent/guardian during an 8-day follow-up period after each vaccination.

Unsolicited adverse events (AEs) within 30-day follow-up period after each dose were recorded.

SAEs were recorded from enrolment up to and including 31 days after dose 2.

The **primary endpoint** was the occurrence of any Grade 3 symptoms within 8 days after vaccination, including extensive limb swellings.

Immunogenicity:

Blood samples were obtained prior to the first dose and approximately one month after each dose. Antibody level against HAV was obtained from all blood samples. Measurement of antibody levels of anti-diphtheria and anti-tetanus toxoid, anti-PT, anti-PRN, anti-FHA, anti-PRP, anti-poliovirus types 1, 2 and 3 were obtained prior to and one month after dose 1.

Antibody levels against MenC (SBA-MenC and anti-PSC) and Protein D antibody concentrations were obtained prior to and one month after dose 1 for Groups 1 and 3.

The following definitions were used:

- Seroprotection status was defined for anti-D and anti-T (titers ≥ 0.1 IU/ml), for anti-polio types 1, 2, and 3 (defined for all three as titers ≥ 8), for anti-PRP (≥ 0.15 mcg/ml and ≥ 1.0 mcg/ml)
- Seropositivity was defined for anti-PT, anti-FHA and anti-PRN (concentration ≥5 EL.U/ml), anti-HAV (concentration ≥ 33 mIU/ml), anti-PSC (concentration ≥ 0.300 mcg/ml), anti-Protein D (concentration ≥ 100 EL.U/ml) and SBA-MenC (antibody titre ≥ 1:8).
- Response rates for pertussis antigens PT, FHA and PRN were defined as the appearance of antibodies in subjects who were initially seronegative, or at least a 2 fold increase from pre- to post-vaccination antibody titers in those who were initially seropositive [ie. ≥ 5 EL.U/ml]).

Statistical methods:

All analyses were descriptive; primary analyses were based on the ATP cohorts.

Reactogenicity:

Reactogenicity/safety was analyzed separately for each dose. The percentage of subjects reporting any symptoms within the 8 days following vaccination and their exact 95% confidence interval (CI) were computed by group according to the type of symptoms, their intensity and relationship to vaccination. In addition the difference between groups with respect to the percentage of subjects reporting at least one Grade 3 symptom (solicited or unsolicited) after dose 1 was evaluated through exact 90% CI.

SAEs and discontinuations due to adverse events were also described.

Immunogenicity:

An interim analysis was performed on cleaned data available up to one month after the administration of the first vaccine dose. The results were kept in-house and not shared with the investigational site until the study was completed.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** **Name of Active Substance:** Diphtheria and tetanus toxoids, PRP, PT, PRN, FHA, poliovirus types 1, 2, 3, HAV, polysaccharide C-protein D conjugate	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Prior to and one month after dose 1, in all groups, seropositivity/seroprotection rates, GMT/Cs and their 95 % CI were tabulated for anti-diphtheria, anti tetanus, anti-PT, anti-FHA, anti-PRN, anti-poliovirus types 1, 2 and 3 and anti-PRP antibodies. The distribution of each antibody concentrations/titres post vaccination was investigated using Reverse Cumulative Curves (RCC). The vaccine response rates to the pertussis antigens (PT, FHA and PRN) and their exact 95% CI were also tabulated for each group. For **Groups 1** and **3**, prior to and one month after vaccination, seropositivity and GMT/Cs with their 95% CI were calculated for SBA-MenC, anti-PSC and anti-Protein D antibodies. The distribution of antibody titres/concentrations post vaccination was investigated using RCCs.
One month after the second HAV vaccine dose, anti-HAV seropositivity rates and GMCs with 95% CI were calculated. The distribution of anti-HAV concentrations was plotted using RCC.

SUMMARY-CONCLUSIONS :

Reactogenicity Results:

- Following dose 1:
  - The percentage of subjects reporting Grade 3 solicited/unsolicited symptoms during the 8-day follow-up period was similar in all three groups. Grade 3 local symptoms occurred in 17.8% to 20.5% of subjects per group, and Grade 3 general symptoms occurred in 6.8% to 12.3% of subjects per group.
  - Redness and pain were the most common solicited local symptoms reported.
  - Few Grade 3 solicited general symptoms were reported; Grade 3 fever (> 39 °C, as measured by axillary/oral route) occurred in 3.1% to 4.8% of subjects per group.
  - Extensive limb swelling reports were completed for 39 subject following dose 1 (12 in Group 1, 13 in Group 2, 14 in Group 3).
- Following HAV dose 2:
  - The percentage of subjects reporting Grade 3 solicited/unsolicited symptoms during the 8-day follow-up period was low in all groups (0.6% in each group).
  - No extensive limb swelling reports were made following HAV dose 2.
- *Serious Adverse Events:* Forty-two (8 in Group 1, 19 in Group 2 and 15 in Group 3) SAEs were reported during the study. Of these, nine (2 in Group 1, 3 in Group 2 and 4 in Group 3) were reported within one month after dose 1 and six (1 in Group 1, 2 in Group 2 and 3 in Group 3) were reported within one month after dose 2 of HAV. Twenty-seven SAEs were reported 30 days after dose 1 but before HAV dose 2 and none were reported 30 days after second dose of HAV. All SAEs were assessed by the investigator as "not related" to vaccination.
- There were no drop-outs due to SAEs or an adverse events.

Difference between groups in terms of percentage of subjects with any Grade 3 symptoms (solicited/unsolicited) during the 8-day follow-up period after dose 1 (ATP safety cohort)

N	Rate (%)	N	Rate (%)	Difference (%)	90% CI	
Group 1		Group 3		(Group 3 minus Group 1)		
41	24.8	42	26.1	1.24	-7.50	10.35
Group 2		Group 3		(Group 3 minus Group 2)		
42	25.8	42	26.1	0.32	-8.57	9.40

Group 1: DTPaHAV-IPV/Hib-MenC; Group 2: DTPa-HAV-IPV/Hib; Group 3: DTPa-IPV/Hib+HAV
N: Number of subjects with at least one documented dose
Rate (%): percentage of subjects experiencing any Grade 3 solicited symptom during the 8-day follow-up period after vaccination; 90% CI: Exact 90% confidence interval

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** **Name of Active Substance:** Diphtheria and tetanus toxoids, PRP, PT, PRN, FHA, poliovirus types 1, 2, 3, HAV, polysaccharide C-protein D conjugate	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Incidence of any and Grade 3 solicited local symptoms during the 8-day follow-up period after dose 1 (ATP safety cohort)

Symptoms		Group 1 (N = 165) DTPa-HAV-IPV/Hib-MenC				Group 2 (N = 163) DTPa-HAV-IPV/Hib				Group 3 (N = 161) DTPa- IPV/Hib				Group 3 (N = 161) *Havrix*™			
		n	%	95% CI		n	%	95% CI		n	%	95% CI		n	%	95% CI	
Pain	Total	98	59.4	51.5	67.0	112	68.7	61.0	75.7	94	58.4	50.4	66.1	44	27.3	20.6	34.9
	Grade 3	14	8.5	4.7	13.8	13	8.0	4.3	13.3	12	7.5	3.9	12.7	7	4.3	1.8	8.8
Redness	Total	105	63.6	55.8	71.0	112	68.7	61.0	75.7	95	59.0	51.0	66.7	45	28.0	21.2	35.6
	> 20 mm	47	28.5	21.7	36.0	41	25.2	18.7	32.5	47	29.2	22.3	36.9	4	2.5	0.7	6.2
	> 50 mm	17	10.3	6.1	16.0	16	9.8	5.7	15.5	19	11.8	7.3	17.8	0	0.0	0.0	2.3
Swelling	Total	76	46.1	38.3	54.0	85	52.1	44.2	60.0	72	44.7	36.9	52.7	21	13.0	8.3	19.2
	> 20 mm	37	22.4	16.3	29.6	30	18.4	12.8	25.2	39	24.2	17.8	31.6	8	5.0	2.2	9.6
	> 50 mm	6	3.6	1.3	7.7	9	5.5	2.6	10.2	10	6.2	3.0	11.1	0	0.0	0.0	2.2

Incidence of any, Grade 3 and 'PB'/'SU' solicited general symptoms during the 8-day follow-up period after dose 1 (ATP safety cohort)

Symptoms		Group 1 (N = 165) DTPa-HAV-IPV/Hib-MenC				Group 2 (N = 163) DTPa-HAV-IPV/Hib				Group 3 (N = 161) DTPa- IPV/Hib + *Havrix*™			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
Fever	Any	62	37.6	30.2	45.4	63	38.7	31.1	46.6	63	39.1	31.5	47.1
	Grade 3	8	4.8	2.1	9.3	6	3.7	1.4	7.8	5	3.1	1.0	7.1
	'PB'/'SU'	60	36.4	29.0	44.2	62	38.0	30.6	46.0	60	37.3	29.8	45.2
Drowsiness	Any	59	35.8	28.5	43.6	70	42.9	35.2	50.9	57	35.4	28.0	43.3
	Grade 3	3	1.8	0.4	5.2	4	2.5	0.7	6.2	5	3.1	1.0	7.1
	'PB'/'SU'	58	35.2	27.9	43.0	70	42.9	35.2	50.9	55	34.2	26.9	42.0
Irritability	Any	92	55.8	47.8	63.5	107	65.6	57.8	72.9	96	59.6	51.6	67.3
	Grade 3	2	1.2	0.1	4.3	7	4.3	1.7	8.6	2	1.2	0.2	4.4
	'PB'/'SU'	87	52.7	44.8	60.5	107	65.6	57.8	72.9	94	58.4	50.4	66.1
Loss of appetite	Any	67	40.6	33.0	48.5	72	44.2	36.4	52.1	59	36.6	29.2	44.6
	Grade 3	3	1.8	0.4	5.2	9	5.5	2.6	10.2	1	0.6	0.0	3.4
	'PB'/'SU'	62	37.6	30.2	45.4	69	42.3	34.6	50.3	53	32.9	25.7	40.8

Group 1: DTPa-HAV-IPV/Hib-MenC; Group 2: DTPa-HAV-IPV/Hib; Group 3: DTPa-IPV/Hib + HAV
N: number of subjects with at least one symptom sheet completed
n (%): number (percentage) of subjects reporting a specified symptom
Redness or swelling diameter > 50 mm = Grade 3
Grade 3 Fever: oral or axillary temperature > 39°C
Grade 3 drowsiness or loss of appetite: symptom that prevented normal activity
'PB'/'SU': symptoms determined by the investigator to have 'probable'/'suspected' relationship to study vaccine
95% CI: Exact 95% confidence interval, lower and upper limits

Immunogenicity Results:

One month after the dose 1:

- All subjects in Group 3 and 99.4% subjects in Groups 1 and 2 were seroprotected in terms of anti-diphtheria antibodies. All subjects in the three groups were seroprotected in terms of anti-tetanus antibodies and anti-poliovirus antibodies.
- The vaccine response to pertussis antigens ranged between 95.4%-100% and was similar in all three groups. All subjects who were seronegative prior to the booster vaccination showed a vaccine response.
- 99.4% subjects in Group 1 and 98.7% subjects in Groups 2 and 3 had anti-PRP antibody concentrations ≥ 1 mcg/ml.
- In Group 1 (DTPa-HAV-IPV/Hib-MenC, the only group receiving the MenC vaccine), 55 % of the subjects achieved SBA-MenC titre ≥ 1:8, which is below published data on the immune response for new meningococcal serogroup C conjugate vaccines in toddlers.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium Name of Finished Product: Name of Active Substance: Diphtheria and tetanus toxoids, PRP, PT, PRN, FHA, poliovirus types 1, 2, 3, HAV, polysaccharide C-protein D conjugate	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	(for national authority only)

- The immune response in terms of seropositivity rates and GMCs for anti-HAV antibodies was lower in Groups 1 and 2 than in Group 3.

One month after HAV dose 2:

- Most subjects in Groups 1 and 2 were seropositive after the second dose of HAV, but GMCs were still lower than for Group 3.

Anti-HAV antibodies: Seropositivity rates and GMCs prior to first dose and one month after each of the two doses for the Total cohort are as follows:

Group	Timing	N	≥ 33 mIU/ml				GMC (mIU/ml)		
			n	%	95% CI		mIU/ml	95% CI	
1	Pre	159	1	0.6	0.0	3.5	16.584	16.418	16.751
	Post vac. 1	156	73	46.8	38.8	54.9	38.631	32.802	45.496
	Post vac. 2	150	147	98.0	94.3	99.6	648.850	530.603	793.447
2	Pre	156	1	0.6	0.0	3.5	16.710	16.297	17.134
	Post vac. 1	155	63	40.6	32.8	48.8	36.741	30.709	43.958
	Post vac. 2	153	151	98.7	95.4	99.8	729.869	607.610	876.729
3	Pre	156	4	2.6	0.7	6.4	17.248	16.490	18.041
	Post vac. 1	154	136	88.3	82.2	92.9	92.585	79.863	107.333
	Post vac. 2	148	148	100.0	97.5	100.0	1446.10	1245.72	1678.70

Group 1: DTPa-HAV-IPV/Hib-MenC + second dose HAV
Group 2: DTPa-HAV-IPV/Hib + second dose HAV
Group 3: DTPa-IPV/Hib + HAV + second dose HAV
N: number of subjects with available results
n (%): number (percentage) of subjects with titres ≥ assay cut off (33 mIU/ml)
95% CI: 95% confidence intervals
Pre: Pre-vaccination
Post vac. 1: One month after dose 1
Post vac. 2: One month after the second HAV dose

Conclusions:

- The study vaccines (DTPa-HAV-IPV mixed with Hib or Hib-MenC) showed a similar reactogenicity profile to the control group (DTPa-IPV/Hib+HAV) in terms of Grade 3 solicited/ unsolicited symptoms and extensive limb swelling occurring within 8 days of vaccination (dose 1).
- There were no major differences in the overall reactogenicity profile between the groups.
- There were no SAEs assessed as 'related' or 'possibly related' to vaccine by the investigator.
- The DTPa-HAV-IPV vaccine mixed with Hib or Hib-MenC vaccine induced a lower response in terms of HAV antibodies (both seropositivity and GMCs were lower than when the HAV vaccine was given as a separate injection). When the second dose of HAV vaccine was given 6 months later, GMCs were still lower in the groups that had received the first HAV dose in combined vaccines.
- The meningococcal serogroup C bactericidal (SBA-MenC) response was below the response obtained with licensed meningococcal serogroup C conjugate vaccines in the group vaccinated with the DTPa-HAV-IPV/Hib-MenC vaccine.
- The immune response of the study vaccines to the other antigens was equivalent to the immune response induced by the control DTPa-IPV/Hib vaccine.

Date of report: 23 July 2002

Document 1

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** **Name of active substance:** *Neisseria meningitidis* capsular polysaccharide C and *Haemophilus influenzae* type b tetanus toxoid conjugates, DTPa, HBV, IPV	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Title of the study : A phase II, open, controlled study to evaluate the persistence and the immune memory induced by a primary vaccination course with GlaxoSmithKline (GSK) Biologicals' meningococcal serogroup C conjugate vaccine (one formulation) and GSK Biologicals' Haemophilus influenzae type b---meningococcal serogroup C conjugate vaccine (two formulations) or Meningitec™ in healthy toddlers aged 12-15 months primed in study 711202/001.

Principal Investigator:	s22 [redacted]
Study Center:	Johannes Gutenberg Universität Langenbeckstr. 1 55101 Mainz, Germany

Publication (reference): Not published as of August 2004

Study period: Study Initiation Date: 31 Jan 2003 Study Completion Date: 24 Jul 2003	**Clinical phase:** II

Objectives:

Primary:

To evaluate the immune memory induced by a three-dose primary vaccination course of GSK Biologicals' meningococcal serogroup C conjugate vaccine (MenC, one formulation) or GSK Biologicals' *Haemophilus influenzae* type b-meningococcal serogroup C conjugate vaccine (Hib-MenC, two formulations) or Meningitec™ by giving meningococcal ACWY plain polysaccharide (one fifth of a dose of Mencevax™ ACWY) concomitantly with Infanrix™ hexa in toddlers aged 12-15 months who participated in study 711202/001.

Secondary:

- To evaluate the persistence of the MenC, Hib and tetanus toxoid immune responses of all subjects primed in study 711202/001 prior to the administration of Mencevax™ ACWY (one fifth of a dose) and Infanrix™ hexa.
- To evaluate the Hib and tetanus toxoid immune responses of a booster dose of GSK Biologicals' Infanrix™ hexa given concomitantly with Mencevax™ ACWY (one fifth of a dose) in toddlers aged 12-15 months who were primed with GSK Biologicals' MenC conjugate vaccine (one formulation) or GSK Biologicals' Hib-MenC conjugate vaccine (two formulations) or Meningitec™ in study 711202/001 or in non-randomized, age-matched subjects not vaccinated with a serogroup C meningococcal vaccine.
- To evaluate the safety and reactogenicity of one fifth of a dose of Mencevax™ ACWY given concomitantly with Infanrix™ hexa in toddlers aged 12-15 months who were primed with GSK Biologicals' MenC conjugate vaccine (one formulation) or GSK Biologicals' Hib-MenC conjugate vaccine (two formulations) or Meningitec™ in study 711202/001 or in non-randomized, age-matched subjects not vaccinated with a serogroup C meningococcal vaccine.

Study design: Open, non-randomized extension of study 711202/001 (MenC-TT-001) conducted in the same centers as the primary study. The study consisted of five groups allocated to two parallel arms as follows:

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** **Name of active substance:** *Neisseria meningitidis* capsular polysaccharide C and *Haemophilus influenzae* type b tetanus toxoid conjugates, DTPa, HBV, IPV	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

In this present study, all subjects in both arms received one-fifth (1/5) of a dose of Mencevax™ ACWY and a concomitant dose of Infanrix™ hexa at 12-15 months of age (Study Month 0). Two blood samples were collected from all subjects (Study Month 0 and Study Month 1).

Arm 1 consisted of four groups from the primary vaccination study 711202/001 who were primed at their age of 3, 4 and 5 months with the following vaccines:

- Group K: MenC (10 µg), non-adsorbed (non-ads), tetanus toxoid (TT) conjugate and Infanrix™ hexa ($MenC_{10}$-TT + Infanrix™ hexa)
- Group L: Hib (10 µg)-MenC (10 µg), non-ads TT conjugate and Infanrix™ penta (Hib_{10}-$MenC_{10}$-TT + Infanrix™ penta)
- Group M: Hib (5 µg)-MenC (5 µg), non-ads, TT conjugate and Infanrix™ penta (Hib_5-$MenC_5$-TT + Infanrix™ penta)
- Group N: Meningitec™ and Infanrix™ hexa (Meningitec™ + Infanrix™ hexa)

The two Hib-MenC-TT vaccine groups (Groups L and M) were kept blinded in the booster study as to the exact formulation of the candidate vaccine.

Arm 2-(Group O) consisted of age-matched subjects not previously vaccinated with a meningococcal serogroup C vaccine (naïve) but who had received routine pediatric vaccines according to the German Permanent Commission on Immunization.

Number of subjects:

Planned: 500
Arm 1: Group K: 100; Group L: 100; Group M: 100; Group N: 100
Arm 2: Group O: 100

Enrolled: 459
Arm 1: Group K: 85; Group L: 89; Group M: 94; Group N: 95
Arm 2: Group O: 96

Completed: 454
Arm 1: Group K: 82; Group L: 89; Group M: 94; Group N: 94
Arm 2: Group O: 95
5 withdrawals, none due to adverse event(s).

Analyzed for Immunogenicity:

- According-to-protocol (ATP) cohort for safety (primary cohort for evaluation of persistence of antibodies elicited by the primary vaccination course in study 711202/001): 448.
- ATP cohort for immunogenicity (primary cohort for evaluation of immune response to the booster): 418

Analyzed for Safety: Total vaccinated cohort (primary cohort for safety analysis): 459

Diagnosis and criteria for inclusion: Healthy toddlers aged 12-15 months, free of obvious health problems as established by medical history and clinical examination:

- Arm 1: who had received at least one dose of the 3-dose vaccination course of a meningococcal serogroup C vaccine (MenC or Hib-MenC) in the study 711202/001.

OR

- Arm 2: who had no previous vaccination with a meningococcal serogroup C vaccine but had completed primary vaccination according to the German STIKO (Staendige Impfkommission Standing Committee on Immunizations) recommendation at least six months before enrolment.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** **Name of active substance:** *Neisseria meningitidis* capsular polysaccharide C and *Haemophilus influenzae* type b tetanus toxoid conjugates, DTPa, HBV, IPV	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Study vaccine, dose, mode of administration, lot no.:

Test product	Formulation (contents per dose)	Route/site	Presentation	Lot
Infanrix™hexa (DTPa-HBV-IPV/Hib) composition				
DTPa-HBV-IPV	Diphtheria toxoid ≥ 30IU (25Lf); Tetanus toxoid ≥ 40IU (10Lf); Pertussis antigens: pertussis toxoid (PT) 25 µg, filamentous haemagglutinin (FHA) 25 µg, pertactin (PRN) 8 µg; Hepatitis B surface antigen (HBsAg): 10 µg; Poliovirus type 1: 40 D antigen units, poliovirus type 2: 8 D antigen units, poliovirus type 3: 32 D antigen units; Phenoxyethanol ≤ 2.5 mg; Aluminium as salt 0.7 mg	IM/ left thigh	Whitish liquid in pre-filled syringe (0.5 ml)	21876B9
Haemophilus influenzae type b (Hib)	Polyribosyl Ribitol Phosphate (PRP) 10 µg conjugated to tetanus toxoid (20-40 µg) Aluminium as salt 120 µg		Lyophilized pellet in monodose vial to be reconstituted with DTPa-HBV-IPV component	Hib425A47
Mencevax™ ACWY	Purified polysaccharides from *Neisseria meningitidis* of serogroups A, C, W135 and Y (content per dose, each: 50 µg; note: only 1/5 dose was administered)*	IM/ right thigh	Lyophilized pellet in monodose vial (0.5 ml after reconstitution with saline diluent supplied in monodose vial)	N391A47

*Dose: One dose of the lyophilized Mencevax™ ACWY was reconstituted with 1.0 ml diluent supplied in two separate vials (each containing 0.5 ml of diluent, lot number: 01B20/22A), and 0.2 ml (1/5 dose) was administered as a separate injection to all subjects.

Duration of treatment: Duration of study was approximately one month for each subject.

Criteria for evaluation:

Immunogenicity: Determination of bactericidal antibody titers against meningococcal C (SBA-MenC) by a bactericidal test (cut-off: a dilution of 1:8) and ELISA measurement of antibodies against meningococcal serogroup C (assay cut-off : 0.3 µg/ml), the Hib polysaccharide PRP (assay cut-off: 0.15 µg/ml) and tetanus toxoid (assay cut-off: 0.1 IU/ml) in blood samples obtained prior to vaccination and approximately one month after vaccination in all subjects.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** **Name of active substance:** *Neisseria meningitidis* capsular polysaccharide C and *Haemophilus influenzae* type b tetanus toxoid conjugates, DTPa, HBV, IPV	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Immunogenicity endpoints:

- Serum bactericidal activity against *N. meningitidis* serogroup C
  - SBA-MenC titer ≥1:8 (seropositivity)
  - SBA-MenC titer ≥1:128
- *N. meningitidis* serogroup C antibody (anti-PSC) concentration ≥0.30 µg/ml (seropositivity)
- Anti-PSC concentration ≥2.0 µg/ml
- Hib polysaccharide PRP antibody (anti-PRP) concentration ≥0.15 µg/ml (seroprotection)
- Anti-PRP concentration ≥1.0 µg/ml (seroprotection)
- Tetanus toxoid antibody concentration (anti-tetanus) ≥0.1 IU/ml (seroprotection)
- SBA-MenC titer
- Anti-PSC concentration
- Anti-PRP concentration
- Anti-tetanus concentration

Reactogenicity and safety endpoints:

- Occurrence of any local or general solicited adverse events during the solicited 4-day (Day 0 to Day 3) follow-up period following vaccination.
- Occurrence of unsolicited non-serious adverse events within 31 days (Day 0 to Day 30) following vaccination.
- Occurrence of any serious adverse event within 31 days following vaccination.

The occurrence of extensive swelling of the injected limb (defined as swelling with a diameter >50 mm, noticeable diffuse swelling or noticeable increase of limb circumference) was recorded in detail.

Statistical methods:

Demographics: Determination of mean age in months (with median, range and standard deviation [SD]), and racial and gender composition of the ATP and Total vaccinated cohorts.

Immunogenicity:

Two analyses of immunogenicity were performed based on the ATP cohort for immunogenicity (for analyses of immune memory and booster response) or the ATP cohort for safety (for analysis of persistence). These included:

Evaluation of immune memory for MenC and booster response for Hib and Tetanus (before and one month after administration of 1/5 dose of the plain polysaccharide vaccine):

- Determination of geometric mean titers and concentrations (GMTs and GMCs) with 95% confidence intervals (95% CI)
- Determination of the percentage of subjects with antibody titer/concentration above the proposed cut-offs with exact 95% CI (seropositivity/seroprotection rates)
- Investigation of antibody titers/concentration after vaccination using reverse cumulative curves
- Computation of standardized asymptotic 95% CI for the difference in seropositivity/seroprotection rate between each primed group (Groups K, L, M and N) and the unprimed group (Group O)
- Determination of the geometric mean of individual ratio of SBA-MenC titer over anti-PSC concentration, with 95% CI
- Determination of the 95% CI for the post-vaccination GMT/C ratio between the groups K, L, M and the control group N for anti-PRP and anti-tetanus and between each primed group (Groups K, L, M and N) and the unprimed group (Group O) for SBA-MenC and anti-PSC using an ANOVA model

Document 1

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** **Name of active substance:** *Neisseria meningitidis* capsular polysaccharide C and *Haemophilus influenzae* type b tetanus toxoid conjugates, DTPa, HBV, IPV	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Evaluation of persistence (one month after priming and before administration of 1/5 dose of the plain polysaccharide vaccine and Infanrix™ hexa [pre-vaccination]):

- Determination of GMTs and GMCs with 95% CI
- Determination of percentage of subjects with antibody titer/concentration above the proposed cut-offs with exact 95% CI (seropositivity/seroprotection rates)
- Investigation of pre-vaccination antibody titers/concentration using reverse cumulative curves
- Determination of standardized asymptotic 95% CI for the difference in pre-vaccination percentage of subjects with antibody titer/concentration above the proposed cut-offs between the control group primed with Meningitec™ and Infanrix™ hexa (Group N) and each of the groups primed with a test vaccine regimen in study 711202/001 (Groups K, L and M)
- Determination of the 95% CI for the pre-vaccination GMT or GMC ratio between the control group (Group N) and each of the groups primed with a test vaccine regimen (Groups K, L and M) using an ANOVA model

Reactogenicity/safety:

The analysis of safety was based on the Total vaccinated cohort and included:

- Calculation of the incidences of local and general adverse events (solicited, unsolicited) including those rated Grade 3 and those with a reasonable possibility that the vaccine contributed to the adverse event with exact 95% CI after vaccination. Unsolicited adverse events were coded by the World Health Organization (WHO) body systems/preferred terms. Extensive swelling and serious adverse events and discontinuation due to adverse events were described.
- Calculation of the percentage of subjects who received any concomitant medication, any antipyretic and prophylactic antipyretic within the 4-day follow-up (Days 0 to 3) after vaccination with exact 95% CI. Concomitant medications were coded by the WHO drug dictionary.

SUMMARY/CONCLUSIONS:

Demography Results: The mean age of the total vaccinated cohort at the time of the study vaccination was 12.8 months ± 1.0 month SD. The majority of subjects (443/459, representing 96.5%) were of the white race and the male/female ratio was 1.1/1. Arm 1 (primed in the study 711202/001) was considered representative of the subjects randomized to those four groups in the primary vaccination study since 87% of those eligible were enrolled in this present study.

Immunogenicity Results: **Immune memory (ATP cohort for immunogenicity)**

Administration of 1/5 dose of the plain polysaccharide ACWY vaccine elicited very high SBA-MenC titer in all four primed groups with 98.7-100% and 97.5-100% of subjects primed with a candidate vaccine regimen exhibiting titers ≥1:8 and ≥1:128, respectively. In the group primed with the Meningitec™ regimen, there was a trend for a lower percentage of subjects with titers ≥1:128 (91.8%). In comparison, 17.6% of unprimed subjects had SBA MenC titers ≥ 1:8 and ≥1:128.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** **Name of active substance:** *Neisseria meningitidis* capsular polysaccharide C and *Haemophilus influenzae* type b tetanus toxoid conjugates, DTPa, HBV, IPV	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Calculation of the 95% CI for the GMT/C ratio between the groups supported the obvious higher antibody response in the primed groups as compared to the naïve control group which showed that immune memory was induced by all four primary vaccines. In addition, SBA-MenC GMTs achieved in the groups primed with $MenC_{10}$-TT and Hib_5-$MenC_5$-TT and the anti-PSC GMCs with the three candidate vaccines were higher than in the Meningitec™ primed group (Synopsis Table 1).

Synopsis Table 1: SBA-MenC titers and anti-PSC antibody concentration after booster vaccination: GMT/C and ratio between groups

Antibody	Group	N	GMT/C	95%CI		Group ratio and 95% CI			
				LL	UL	Ratio	Value	95% CI LL	95% CI UL
SBA-MenC	K	71	3508.9	2580.1	4772.2	K/O	378.98	235.66	609.44
	L	79	2530.1	1831.7	3494.7	L/O	273.25	172.27	433.44
	M	81	5385.4	4425.0	6554.2	M/O	581.63	367.80	919.78
	N	85	1552.6	1044.4	2307.9	N/O	167.68	106.64	263.65
	O	91	9.3	6.3	13.6	—	—	—	—
Anti-PSC	K	70	28.10	22.59	34.95	K/O	9.22	6.73	12.63
	L	71	30.01	24.09	37.38	L/O	9.85	7.20	13.47
	M	76	34.58	29.10	41.09	M/O	11.35	8.34	15.44
	N	78	16.59	12.98	21.21	N/O	5.44	4.01	7.39
	O	94	3.05	2.36	3.93	—	—	—	—

Group K: subjects primed with $MenC_{10}$-TT + Infanrix™ hexa; Group L: subjects primed with Hib_{10}-$MenC_{10}$-TT + Infanrix™ penta; Group M: subjects primed with Hib_5-$MenC_5$-TT + Infanrix™ penta; Group N: subjects primed with Meningitec™ + Infanrix™ hexa; Group O: control subjects (i.e. subjects not primed with MenC conjugate vaccine)
N: number of subjects with available results

Synopsis Table 2: Geometric mean ratio (GMR) for SBA-MenC titer / anti-PSC concentration

Group	Timing	N	GMR	LL	UL
K	Pre	70	49.470	34.939	70.044
	Post	66	126.138	101.419	156.882
L	Pre	76	36.528	25.849	51.621
	Post	70	90.200	70.153	115.975
M	Pre	77	51.298	36.478	72.139
	Post	74	164.950	139.304	195.318
N	Pre	84	22.571	16.521	30.837
	Post	76	90.168	67.757	119.991
O	Pre	3	91.634	0.651	12889.8
	Post	87	2.708	1.767	4.149

In all four primed groups (Groups K, L, M and N), the GMR increased significantly from pre to post booster vaccination indicating the presence of antibody maturation and functionality. GMR in the Group M (primed with Hib_5-$MenC_5$-TT) was higher than in the Group N (primed with Meningitec™).

Pre: blood sample obtained just prior to administration of study vaccination; Post: blood sample obtained one month after booster

Persistence of the MenC, Hib and tetanus toxoid immune responses of all subjects primed in study 711202/001: In terms of the percentage of subjects with antibody titer/concentration above the pre-defined cut-offs, antibody persistence at the age of 12-15 months was similar in the four groups primed in the 3rd, 4th and 5th month of age with the exception of anti-PSC concentration ≥2µg/ml (Hib_{10}-$MenC_{10}$-TT significantly lower than Meningitec™) and anti-PRP concentration ≥.0.15µg/ml and ≥1µg/ml (both the Hib-MenC primed groups significantly higher than Meningitec™). Data are shown hereafter (Table 3).

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** **Name of active substance:** *Neisseria meningitidis* capsular polysaccharide C and *Haemophilus influenzae* type b tetanus toxoid conjugates, DTPa, HBV, IPV	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Synopsis Table 3: Persistence at 12-15 months of age just prior to administration of the booster vaccines (ATP cohort for safety)

Endpoints	Group	N	%	Group	N	%	Difference	Value %	LL	UL
SBA-MenC ≥1:8	K	79	88.6	N	91	80.2	N – K	-8.4	-19.4	2.8
	L	84	93.3	N	91	80.2	N – L	-3.1	-14.6	8.6
	M	85	87.1	N	91	80.2	N – M	-6.8	-17.9	4.3
SBA-MenC ≥1:128	K	79	65.8	N	91	51.6	N – K	-14.2	-28.3	0.7
	L	84	56.0	N	91	51.6	N – L	-4.3	-18.8	10.4
	M	85	64.7	N	91	51.6	N – M	-13.1	-27.1	1.5
anti-PSC ≥0.3µg/ml	K	79	100.0	N	91	100.0	N – K	0.0	-4.1	4.6
	L	84	100.0	N	91	100.0	N – L	0.0	-4.1	4.4
	M	88	98.9	N	91	100.0	N – M	1.1	-2.9	6.2
anti-PSC ≥2µg/ml	K	79	72.2	N	91	81.3	N – K	9.2	-3.5	22.0
	L	84	64.3	N	91	81.3	N – L	17.0	3.9	29.9*
	M	88	64.3	N	91	81.3	N – M	8.6	-3.8	20.9
anti-PRP ≥0.15µg/ml	K	81	88.9	N	91	85.7	N – K	-3.2	-13.4	7.3
	L	86	96.5	N	91	85.7	N – L	-10.8	-19.9	-2.6*
	M	90	98.9	N	91	85.7	N – M	-13.2	-22.0	-6.3*
anti-PRP ≥1µg/ml	K	81	33.3	N	91	28.6	N – M	-4.8	-18.6	9.0
	L	86	55.8	N	91	28.6	N – K	-27.2	-40.6	-12.8*
	M	90	74.4	N	91	28.6	N – L	-45.9	-57.8	-32.1*
anti-tetanus ≥0.1 IU/ml	K	81	100.0	N	91	96.7	N – M	-3.3	-9.2	1.3
	L	86	100.0	N	91	96.7	N – K	-3.3	-9.2	1.0
	M	90	100.0	N	91	96.7	N – L	-3.3	-9.2	0.9

Group K: subjects primed with $MenC_{10}$-TT + Infanrix™ hexa; Group L: subjects primed with Hib_{10}-$MenC_{10}$-TT + Infanrix™ penta; Group M: subjects primed with Hib_5-$MenC_5$-TT + Infanrix™ penta; Group N: subjects primed with Meningitec™ + Infanrix™ hexa; N: number of subjects with available results

* indicates a statistically significant difference

- SBA-MenC: GMTs in both the Hib_{10}-$MenC_{10}$-TT group (108.9) and Hib_5-$MenC_5$-TT group (159.3) were similar to the Meningitec™ primed group (104.0) while GMT in the $MenC_{10}$-TT primed group (189.1) was statistically higher as compared to the Meningitec™ primed group.
- Anti-PSC: GMCs in both the Hib_{10}-$MenC_{10}$-TT group (2.8 µg/ml) and Hib_5-$MenC_5$-TT group (3.2 µg/ml) were statistically lower compared to the Meningitec™ group (4.5 µg/ml); GMC in the $MenC_{10}$-TT group (3.9 µg/ml) was not. .
- Anti-PRP: GMCs in both the Hib_{10}-$MenC_{10}$-TT group (1.2 µg/ml) and Hib_5-$MenC_5$-TT group (2.1 µg/ml) were statistically higher compared to the Meningitec™ group (0.5 µg/ml); GMC in the $MenC_{10}$-TT group (0.7 µg/ml) was not.
- Anti-tetanus: GMCs in all three candidate vaccine groups ($MenC_{10}$-TT: 0.8 IU/ml; Hib_{10}-$MenC_{10}$-TT: 0.7 IU/ml; Hib_5-$MenC_5$-TT: 0.9 IU/ml) were statistically higher compared to the Meningitec™ group (0.4 IU/ml).

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** **Name of active substance:** *Neisseria meningitidis* capsular polysaccharide C and *Haemophilus influenzae* type b tetanus toxoid conjugates, DTPa, HBV, IPV	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Booster immune response (ATP cohort for immunogenicity):

- Anti-PRP: Antibody response to administration of the booster dose of Infanrix™ hexa vaccine in terms of the percentages of subjects with anti PRP concentrations ≥0.15 µg/ml (98.8-100%) and ≥1 µg/ml (96.5-100%) was within the same range in all groups. GMC of anti-PRP in the Hib_5-$MenC_5$-TT + Infanrix™ penta primed group (73.2 µg/ml) was higher compared to the Meningitec™ group (34.3 µg/ml).
- Anti-tetanus: One month after booster administration, all subjects in all groups had seroprotective concentrations of anti-tetanus antibodies. GMCs of anti-tetanus were within the same range in the three groups primed with a candidate vaccine regimen and higher in all three groups as compared to the group primed with Meningitec™ + Infanrix™ hexa regimen.

Safety Results: **The safety analysis was performed on the Total vaccinated cohort.**
The incidence and nature of symptoms reported during the 31 days follow-up period after vaccination was comparable in all five groups. Overall, 62.5-70.6% of subjects presented with at least one solicited and/or unsolicited symptom (Synopsis Table 3).

Synopsis Table 3: Incidence and nature of symptoms and grade 3 symptoms (solicited and unsolicited) reported within one month (Day 0-31) after booster vaccination

Group	N	Any symptom (%)		General symptom (%)		Local symptom (%)	
		Overall	Grade 3	Overall	Grade 3	Overall	Grade 3
K	85	70.6	9.4	61.2	5.9	45.9	3.5
L	89	69.7	4.5	56.2	1.1	46.1	3.4
M	94	70.2	13.8	56.4	5.3	44.7	8.5
N	95	70.5	8.4	60.0	0.0	45.3	8.4
O	96	62.5	6.3	51.0	2.1	51.0	4.2

Group K: subjects primed with $MenC_{10}$-TT + Infanrix™ hexa; Group L: subjects primed with Hib_{10}-$MenC^{10}$-TT + Infanrix™ penta; Group M: subjects primed with Hib_5-$MenC_5$-TT + Infanrix™ penta; Group N: subjects primed with Meningitec™ + Infanrix™ hexa; Group O: naïve control subjects
N : number of subjects having received at least one dose; %: percentage of subjects presenting at least one type of symptom during the 31 days follow-up period (day 0 to day 30)

In the 4-day follow-up post-vaccination:

- Solicited local injection site symptoms reported occurred at similar frequencies and redness (reported in 36.5-42.7% of subjects) was the most frequently reported solicited local symptom in all five groups. For each solicited local symptom, clinically significant events (Grade 3 in intensity) were reported in 6.4% of subjects or less and occurred at similar frequencies in the five groups.
- The percentage of subjects for whom each solicited general symptom was reported was within the same range overall in all five groups. Drowsiness (reported in 25.9-31.6% of subjects) and irritability (reported in 24.5-32.6% of subjects) were the most frequently reported solicited general symptoms. For each solicited general symptom, clinically significant events (Grade 3 in intensity) were rare (reported in 2.4% of subjects or less in the five groups).
- Grade 3 fever (>40.0°C) was reported in only two subjects; neither event was considered causally related to vaccination. There were no discernable differences in the occurrence of fever at any level across the five groups (Synopsis Table 5).

Document 1

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** **Name of active substance:** *Neisseria meningitidis* capsular polysaccharide C and *Haemophilus influenzae* type b tetanus toxoid conjugates, DTPa, HBV, IPV	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Synopsis Table 5: Incidence of fever reported within the 4-day follow-up after booster vaccination

Group	N	Any fever (%)	>39.5°C (%)	>40.0°C (%)	>40.0°C *Related (%)
K	85	21.2	0.0	0.0	0.0
L	89	25.8	0.0	0.0	0.0
M	94	25.5	3.2	2.1	0.0
N	95	18.9	0.0	0.0	0.0
O	96	20.8	0.0	0.0	0.0

Any fever: rectal temperature≥38.0°C

- Extensive swelling including at least one adjacent joint was not reported during the 31 day follow-up period (Day 0-30).
- The use of antipyretic/analgesic medication was low and comparable in the five groups during the 31 day follow-up period (Day 0-30). Frequency of use ranged from 1.0% to 3.2%. No subject received a prophylactic antipyretic.
- The incidence of subjects with at least one unsolicited symptom during the 31 day follow-up period (Day 0-30) ranged from 13.5% (95% CI [7.2,22.4]) to 31.8% (95% CI [22.1,42.8]). Only two subjects (both in Group K primed with $MenC_{10}$-TT + Infanrix™ hexa) experienced an unsolicited symptom attributed a Grade 3 in intensity; neither of the events was determined by the investigator to be causally related to vaccination.

Serious Adverse Events: Serious adverse events were reported in four subjects during the course of the study. None were determined by the investigator to be causally related to vaccination and all resolved without sequelae.

Conclusions:

1. Primary Conclusion

The three candidate meningococcal serogroup C conjugate vaccines (MenC-TT, one formulation, and the Hib-MenC-TT, two formulations) as well as Meningitec™ given as a three-dose primary vaccination course to infants in their 3rd, 4th and 5th month of life (study 711202/001) induced immune memory. This was shown by the marked increases in SBA-MenC titers and anti-PSC antibody concentrations in response to 1/5 dose of meningococcal ACWY plain polysaccharide vaccine as compared to naïve control subjects (i.e. not primed with a meningococcal serogroup C conjugate vaccine). For the two groups for which SBA-MenC was retested with the same methodology at post 3 as at post booster (Hib_5-$MenC_5$-TT and Meningitec™), the increase in geometric mean of the individual ratio of SBA-MenC over anti-PSC from post-primary vaccination to post-booster also suggest the presence of maturation of antibody response and functionality. In addition, SBA-MenC GMTs achieved in the groups primed with $MenC_{10}$-TT and Hib_5-$MenC_5$-TT and the anti-PSC GMCs achieved with the three candidate vaccines were higher than with Meningitec™.

Continued: Secondary conclusions overleaf

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** **Name of active substance:** *Neisseria meningitidis* capsular polysaccharide C and *Haemophilus influenzae* type b tetanus toxoid conjugates, DTPa, HBV, IPV	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

2. Secondary Conclusions

- Despite a lower SBA-MenC GMT one month post primary vaccination in the three candidate vaccine groups when compared with the Meningitec™ group, SBA-MenC GMTs at 12-15 months of age were similar (for the Hib_{10}-$MenC_{10}$-TT primed groups) or higher (for the Hib_5-$MenC_5$-TT and $MenC_{10}$-TT primed groups) than the Meningitec™ group. Overall, the persistence of antibodies was good at the age of 12-15 months: more than 80% of subjects retained SBA-MenC titers ≥1:8 and 98.9-100% of subjects in all four MenC primed groups retained anti-PSC concentrations ≥0.3 µg/ml. The percentages of subjects with anti-PRP concentrations ≥0.15 and ≥1.0 µg/ml and anti-PRP GMCs were higher in both the Hib_5-$MenC_5$-TT and Hib_{10}-$MenC_{10}$-TT primed groups compared to the Meningitec™ primed group.
- Administration of the Infanrix™ hexa booster elicited similar antibody responses in terms of seroprotective concentrations of anti-PRP and anti-tetanus. While increases in GMCs were vigorous for both Hib and tetanus antibodies in all groups, GMC of anti-PRP in the group primed with Hib_5-$MenC_5$-TT + Infanrix™ penta and GMCs of anti-tetanus in all three groups primed with a candidate vaccine regimen were higher than observed in the Meningitec™ + Infanrix™ hexa primed group.
- A booster of 1/5 dose of Mencevax™ ACWY given concomitantly with Infanrix™ hexa in subjects primed in the 711202/001 study (groups primed with $MenC_{10}$-TT + Infanrix™ hexa, Hib-MenC-TT + Infanrix™ penta or Meningitec™ + Infanrix™ hexa) was safe and well tolerated; the reactogenicity profile in the groups primed with three candidate vaccine groups was similar to that observed in the group primed with Meningitec™.

Date of report: August 2004

GlaxoSmithKline

CONFIDENTIAL

Category 1 Application

Changes to Product Information - Large swelling reactions

INFANRIX®
INFANRIX®-HIB
INFANRIX®-IPV
INFANRIX®-PENTA
INFANRIX®-HEXA

Module I – Administrative Information and Prescribing Information

VOLUME 1 of 1

Refer Company Letter of: 21.10.2005

Application No: 2005/2446/2

Copy 4 of 4

October 2005

Category 1 Application
Changes to Product information – Large swelling reactions
INFANRIX®, INFANRIX®-HIB, INFANRIX®-IPV, INFANRIX®-PENTA, INFANRIX®-HEXA

GlaxoSmithKline

Module 1
Volume 1 of 1
Copy 4 of 4
October 2005

Document 1

Confidential

CATEGORY 1 APPLICATION

Changes to Product Information - Large swelling reactions

INFANRIX®
INFANRIX®-HIB
INFANRIX®-IPV
INFANRIX®-PENTA
INFANRIX®-HEXA

Module I – Administrative Information and Prescribing Information

VOLUME 1 of 1

Copy 4 of 4

All and any information contained in this document is to be regarded as commercial in confidence as it is a trade secret containing unpublished details and results of private research proprietary to GlaxoSmithKline Australia Pty Ltd, the disclosure of which to unauthorised persons (including its competitors) other than in accordance with Section 61 of the Therapeutic Goods Act 1989 (as amended) is prohibited without the express authority of GlaxoSmithKline Australia Pty Ltd.

GlaxoSmithKline Australia Pty Ltd
1061 Mountain Highway
Boronia
Australia 3155

October 2005


MANILLA
WHITE DIVIDERS
5 TAB A4
marbig
RefNo: 37320
Made in China
www.accobrands.com.au

Category 1 Application for changes to the Product Information
Large swelling reactions
Infanrix®, Infanrix®-Hib, Infanrix®-IPV, Infanrix®-Penta and Infanrix®-hexa

COMPLETE CONTENTS OF THE SUBMISSION

Module 1 Administrative Information and Prescribing Information

1.1. Comprehensive Table of Contents

1.2. Application Forms

1.3. Australian Labelling and Packaging

1.3.1. Australian Product Information (PI)
1.3.1.1. Annotated Product Information

1.3.2. Australian Consumer Medicine information (CMI)

1.4. Information about the Experts

1.5. Specific requirements for different types of applications

1.6. Confidentiality Statement

1.7. Statement on availability of Individual Patient Data (IPD)

1.8. Overseas Regulatory Status

1.9. Authorisation to refer to Drug and Plasma Master Files

1.10. Summary of Bioavailability Studies

1.11. GMP Status

1.12. Provisional ARTG Record (PAR)

Module 2 Common Technical Document Summaries

MODULE 2
VOLUME

2.1 COMMON TECHNICAL DOCUMENT TABLE OF CONTENTS (m 2-5)..... N/A

2.2 INTRODUCTION ..... N/A

2.3 QUALITY OVERALL SUMMARY ..... N/A

MODULE 2
VOLUME

2.4 NONCLINICAL OVERVIEW ..... N/A

2.5 CLINICAL OVERVIEW 1
2.5.1 Product Development Rationale 1
2.5.2 Overview of Biopharmaceutics ..... N/A
2.5.3 Overview of Clinical Pharmacology ..... N/A
2.5.4 Overview of Efficacy ..... N/A
2.5.5 Overview of Safety 1
2.5.6 Benefits and Risks Conclusions 1
2.5.7 Literature References 1

2.6 NONCLINICAL SUMMARY ..... N/A

2.7 CLINICAL SUMMARY 1
2.7.1 Summary of Biopharmaceutics and Associated Analytical Methods ..... N/A
2.7.2 Summary of Clinical Pharmacology Studies ..... N/A
2.7.3 Summary of Clinical Efficacy ..... N/A
2.7.4 Summary of Clinical Safety 1
2.7.5 Literature References ..... N/A
2.7.6 Synopses of Individual Studies 1

Module 3 Quality

MODULE 3
VOLUME

3.1 MODULE 3 TABLE OF CONTENTS ..... N/A

3.2 BODY OF DATA ..... N/A

3.3 LITERATURE REFERENCES ..... N/A

Module 4 Non-clinical study reports

MODULE 4
VOLUME

4.1 MODULE 4 TABLE OF CONTENTS ..... N/A

4.2 STUDY REPORTS ..... N/A

4.3 LITERATURE REFERENCES ..... N/A

Module 5 : Clinical Study Reports

The current application for changes to the Product Information to include information on large swelling reactions after booster doses of DTPa-combination vaccines is being submitted for all GSK Infanrix-line vaccines. To facilitate review, one combined dossier is hereby submitted, as the supporting data are identical.

5.1 TABLE OF CONTENTS

MODULE 5
VOLUME

5.1 TABLE OF CONTENTS FOR CLINICAL STUDY REPORTS 1

5.2 TABULAR LISTING OF ALL CLINICAL STUDIES 1

5.3 CLINICAL STUDY REPORTS 1
- 5.3.1 Reports of Biopharmaceutic Studies ..... N/A
- 5.3.2 Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials ..... N/A
- 5.3.3 Reports of Human Pharmacokinetic (PK) Studies ..... N/A
- 5.3.4 Reports of Human Pharmacodynamic (PD) Studies ..... N/A
- 5.3.5 Reports of Efficacy and Safety Studies 1

In order to facilitate review of the clinical documentation, the paper (hard) copy of the dossier contains only the body of the study reports provided in this section. The complete reports, with appendices, are provided on CD ROM. Paper copies of the appendices can be supplied by the Applicant upon request.

- 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication 1

208108/076 (HIB-076): Open, phase III clinical trial to assess the immunogenicity and reactogenicity of SB Biologicals' DTPa vaccine co-administered with one dose of unconjugated Hib vaccine in separate injections or mixed in the same syringe with SB Biologicals' Hib conjugate vaccine to healthy children, 12 to 18 months old, previously vaccinated at the age of 2, 4 and 6 months in study DTPa-HBV-IPV-036 (217744/036).
Principal investigator: [redacted]
Report date: Jul 10, 2000 (amended September 14, 2000) 1

208355/118 (APV-118): Randomised, blinded clinical study to assess the immunogenicity and reactogenicity of SB Biologicals' dTpa and DTPa vaccines and a commercial Td vaccine administered as a booster dose to healthy children 4 to 6 years old, previously vaccinated with four doses of SB Biologicals' DTPa vaccine in the first two years of life.
Principal investigator: [redacted]
Report date: October 15, 1998 1

208355/120 (APV-120): Clinical study of the reactogenicity and immunogenicity of SB Biologicals' DTPa vaccine administered as a booster dose to healthy children 4 to 6 years of age, previously vaccination with four doses of SB Biologicals' DTPa vaccine in the first two years of life.
Principal investigator: [redacted]
Report date: February 2, 1999 1

213503/043 (DTPa-IPV-043): Double-blind clinical study to assess the immunogenicity and reactogenicity of a booster dose of GlaxoSmithKline Biologicals' Hib vaccine, conjugated with one of two tetnus toxoid carriers administered mixed as single injection with GSK Biologicals' DTPa-IPV vaccine at 17 to 19 months of age in infants primed in the study DTPa-IPV-039.
Principal investigators: [redacted] and [redacted]
Report date: January 28, 2002 1

213503/045 (DTPa-IPV-045): Open, randomized, phase IIIb, multi-site, clinical study to compare the immunogenicity and reactogenicity of GSK Biologicals' DTPa-IPV vaccine, with GSK Biologicals' DTPa (Infanrix™) and Aventis MSD's IPV vaccine (Imovax Polio®) administered separately to healthy children 4 to 6 years of age, previously vaccinated with three doses of DTPa and IPV or OPV vaccines during the first year of life in a 3, 5 and 11 to 12 month schedule.
Principal investigators: [redacted]
Report date: December 18, 2002 1

213503/046 (DTPa-IPV-046): Open, randomised phase IIIb, clinical trial to compare the immunogenicity and reactogenicity of GSK Biologicals' DTaP-IPV vaccine (INFANRIX®-IPV), with GSK Biologicals' DTaP (INFANRIX®) and Aventis Pasteur MSD's IPV vaccine (IPOL®) administered separately to healthy children 4 to 6 years of age, previously vaccinated with 4 doses of DTaP and polio vaccine, and co-administered with GSK Biologicals' MMR vaccine (PRIORIX™).
Principal investigators: [redacted]
Report date: March 5, 2004 (amended September 1, 2004) 1

213503/049 (DTPa-IPV-049): An open, multicentre, phase IV booster vaccination study to assess the immunogenicity and reactogenicity of GSK Biologicals' combined Infanrix™-IPV+Hib (DTPa-IPV/Hib) vaccine in healthy children aged 17 to 20 months who completed a three-dose primary vaccination course in study 217744/076 (DTPa-HBV-IPV-076).
Principal investigators: [redacted]
Report date: March 23, 2005 1

217744/058 (DTPa-HBV-IPV-058): Open, randomised, multicentre Phase III clinical trial to assess and to compare the reactogenicity of a booster dose of SB Biologicals' DTPa-HBV-IPV and Hib conjugate vaccines when mixed extemporaneously and administered in a single injection and of SB Biologicals' DTPa-IPV/Hib with or without *Engerix-B*™ vaccines administered in separate injections in 12 to 18 months old healthy children, previously vaccinated at the age of 3, 4 and 5 months in primary vaccination study DTPa-HBV-IPV-039 (217744/039).
Principal investigator: [redacted]
Report date: July 10, 2000 1

217744/059 (DTPa-HBV-IPV-059): Open, multicentre Phase III clinical trial to assess the immunogenicity and reactogenicity of SB Biologicals' DTPa-HBV-IPV and Hib conjugate vaccines when mixed extemporaneously and administered in a single injection as a booster dose to 12 to 18 months old healthy children, previously

vaccinated at the age of 3, 4 and 5 months in primary vaccination study DTPa-HBV-IPV-048 (217744/048), with either three doses of the same vaccines or with three doses of DTPa-IPV/Hib and *Engerix-B*™ vaccines administered in separate injections.
Principal investigator: s22 [redacted]
Report date: July 3, 2000 1

217744/061 (DTPa-HBV-IPV-061): A Phase II, single-blinded randomized comparative study of the safety and immunogenicity of a booster dose of SmithKline Beecham Biologicals' DTPa-HepB-IPV vaccine compared with Infanrix® when both vaccines are co-administered with OmniHIB® between 15 and 18 months of age following primary immunization at the age of 2, 4 and 6 months in the study DTPa-HepB-IPV-044 (CPMS N° 217744/044).
Principal investigators: s2 [redacted] 2
Report date: January 12, 2001 1

217744/062 (DTPa-HBV-IPV-062): Open, multicentre, phase III clinical study to assess the immunogenicity and reactogenicity of SB Biologicals' DTPa-HBV-IPV and Hib conjugate vaccines when mixed extemporaneously and administered in a single injection as a booster dose to 12 to 15 months old healthy children, previously vaccinated at the age of 6, 10 and 14 weeks in primary vaccination study DTPa-HBV-IPV-040 (217744/040), with three doses of the same vaccines either or not following a single dose of SB Biologicals' HBV vaccine (Engerix™-B) at birth.
Principal investigators: s2 [redacted] 2
Report date: August 22, 2000 2

217744/065 (DTPa-HBV-IPV-065): Open, randomized, multicentre, phase III clinical trial to assess the reactogenicity and immunogenicity of a booster dose of GlaxoSmithKline (GSK) Biologicals' DTPa-HBV-IPV/Hib vaccine, co-administered during the same visit with GSK Biologicals' MMR or Varicella vaccine, in children in their second year of life, previously vaccinated in the DTPa-HBV-IPV-039, -041, -043 or --057 primary vaccination studies.
Principal investigators: [redacted]
Report date: August 27, 2004 2

217744/066 (DTPa-HBV-IPV-066): Open, randomized, multicentre, phase III clinical trial to assess the reactogenicity and immunogenicity of a booster dose of GlaxoSmithKline (GSK) Biologicals' DTPa-HBV-IPV/Hib vaccine, co-administered during the same visit with GSK Biologicals' HAV vaccine (*Havrix*™), in children in their second year of life, previously vaccinated in the DTPa-HBV-IPV-039, -041, -043 or --057 primary vaccination studies (CPMS N) 217744/039, 041, 043 or 057).
Principal investigators: [redacted]
Report date: November 28, 2003 2

217744/074 (DTPa-HBV-IPV-074): Open, randomized, multicenter, phase IIIb clinical trial to assess the incidence of high grade fever (≥ 40.0 °C) within 4 days following a booster dose in the second year of life of GlaxoSmithKline (GSK) Biologicals' combined DTPa-HBV-IPV/Hib vaccine (*Infanrix HeXa*™) as

compared to GSK Biologicals' combined DTPa-IPV/Hib (*Infanrix™*-IPV+Hib) and HBV (*Engerix-B™* Kinder) vaccines administered concomitantly in separate injections to children previously primed with licensed vaccines according to the vaccination recommendations currently in place in Germany.
Principal investigator: s22 [redacted]
Report date: June 11, 2002 2

217744/095 (DTPa-HBV-IPV-095): Open, multicentric, phase IV clinical trial to assess the immunogenicity and reactogenicity of GSK Biologicals' DTPa-HBV-IPV/Hib vaccine (Infanrix™ hexa) when given as a booster dose to children aged 11 to 23 months previously primed at 2, 4 and 6 months of age either with Aventis Pasteur's DTPa-HBV-IPV-Hib vaccine (Hexavac™) or GSK Biologicals' DTPa-HBV-IPV/Hib vaccine (Infanrix™ hexa) in study DTPa-HBV-IPV-086.
Principal investigator: s22 [redacted]
Report date: March 10, 2005 2

404286/006 (Hepta-006): A Phase II, open randomized, controlled study to assess the immune memory induced by a primary vaccination course of GlaxoSmithKline Biologicals' (GSK Biologicals') DTPa-HBV-IPV extemporaneously mixed with GSK Biologicals' Hib-MenC by giving meningococcal AC polysaccharide, and the safety, reactogenicity and immunogenicity of a booster dose of GSK Biologicals' DTPa-HBV-IPV extempoaneously mixed with Hib-MenC to toddlers primed in study 404286/001.
Principal investigator: [redacted]
Report date: October 22, 2003 2

455697/001 (DTPa-HAV-IPV-001): Open,randomised, multicentric Phase II clinical trial to assess the immunogenicity and reactogenicity of GSK Biologicals' DTPa-HAV-IPV and Hib-MenC vaccines when mixed extemporaneously and administered as a single booster dose to healthy children, 17 to 20 months of age, previously vaccinated with three doses of GSK Biologicals' DTPa-IPV/Hib vaccines in the DTPa-IPV-039 primary vaccination study.
Principal investigators: [redacted]
Report date: July 23, 2002 2

711202/008 (MenC-TT-008): A phase II, open, controleed study to evaluate the persistence and the immune memory indicued by a primary vaccination course with GlaxoSmithKline (GSK) Biologicals' meningococcal serogroup C conjugate vaccine (one formulation) and GSK Biologicals' Haemophilus influenzae type b-meningococcal serogroup C conjugate vaccine (two formulations) or Meningitec™ in healthy toddlers aged 12-15 months primed in study 711202/001.
Principal investigator: s22 [redacted]
Report date: August 2004 2

5.3.5.2 Study Reports of Uncontrolled Clinical Studies ..... N/A
5.3.5.3 Reports of Analyses of Data from More Than One Study, Including Any Formal Integrated Analyses, Meta-analyses, and Bridging Analyses ..... N/A
5.3.5.4 Other Clinical Study Reports ..... N/A

5.3.6 Reports of Postmarketing Experience 2

5.3.7 Case Report Forms and Individual Patient Listings, When Submitted

Specific CRF pages used to record information on extensive local reactions: 2

5.4 LITERATURE REFERENCES 2

Document 1

Therapeutic Goods Act 1989

TGA Therapeutic Goods Administration

COMMONWEALTH DEPARTMENT OF HEALTH, HOUSING AND COMMUNITY SERVICES

Application – INFANRIX HEXA

(please tick the appropriate box)

☐ **for Registration (including Pharmaceutical Benefits Listing) of Drug Products**

☑ **to vary the Conditions of Registration of Drug Products**

(via Drug Evaluation Branch)

- To ensure this form is correctly completed, please refer to the explanatory guide issued for this application form before applying.
- Send **Original** of this form with a cheque for the appropriate fee(s) and an Enterprise Details form if necessary to:
  Note: Cheques should be made payable to: 'Therapeutic Goods Administration'.

via Courier

The Business Manager
Business Management Unit
Therapeutic Goods Administration
4th Floor, Alexander Building
Furzer Street
Phillip ACT
Australia

via Australia Post

The Business Manager
Business Management Unit
Therapeutic Goods Administration
PO Box 100
Woden ACT 2606
Australia

- Send a **copy** of this form with the Data for Evaluation to:

via Courier

The Director
Drug Evaluation Branch
5th Floor
Alexander Building
Furzer Street
Phillip ACT
Australia

via Australia Post

The Director
Drug Evaluation Branch
Therapeutic Goods Administration
PO Box 100
Woden ACT 2606
Australia

Part 1 - General Details

Sponsor details *(If an individual, provide full name; if a corporation, the registered company name under the Companies Code; or business names under which you propose to trade for the purposes of the Therapeutic Goods Act 1989.)*

Sponsor's business name *(max 100 characters)*

GLAXOSMITHKLINE AUSTRALIA PTY LTD

Sponsor's enterprise identification code

400 10

Enterprise details

- Have you attached a completed "Enterprise Details" form? Yes ☐ No ☑

Payment enclosed *(for payment of relevant fees)* $4,170.00

Sponsor Application and Declaration

- Sponsors should note that the *Therapeutic Goods Act 1989* provides penalties for making statements that are false or misleading in connection with an application for registration of therapeutic goods.

I apply to: *(delete whichever is not applicable)*

- ~~Register (including Pharmaceutical Benefits Listing)~~
- Vary the conditions of registration of

the goods described in this form and declare that the information given is, to the best of my knowledge, current and correct.

To the best of my knowledge, I certify that this application is accompanied by such information and in the required format as will allow the determination of the application (ie. complies with the current NDF guidelines for preparing applications to market drug products and any associated or supplementary guidelines). *(Refer to the Guide for details and Note on page 3 of this form.)*

Signature s22 [redacted]

Date 21 / 10 / 05 (dd / mm / yy)

Name *(please print)* s22 [redacted]

Position/ Relationship to Sponsor s22 [redacted]

If you are not the Sponsor, have you attached a copy of a current "Instrument of Appointment" authorising you to act as a duly appointed agent of the Sponsor. Yes ☑ No ☐

Office Use Only

Receipt number

Charge code

Fee $

Correct fee Yes ☐ No ☐

Enterprise ID

TGAIN

ARTG no.

Document 1

- Complete the authorisation below, or a copy, for each person you have appointed to submit applications for registration, listing or manufacturing licence on your behalf.
- Send the original authorisation to the *Therapeutic Goods Administration*. A copy of the authorisation should be included with each application (or group of applications) submitted by the authorised person on behalf of the enterprise.

Instrument of Appointment

- Please print full name where applicable.

I, s22 [redacted] GLAXOSMITHKLINE AUSTRALIA PTY LTD

being a sponsor or company director or company secretary of a sponsor of therapeutic goods in Australi

hereby appoint s22 [redacted]

as my/the sponsor's duly appointed agent to provide information and make declarations for the purpo of applications as required under the *Therapeutic Goods Act 1989*.

Signature s22 [redacted]

Date 9 / 7 / '02

- **Note:** If an individual person is the sponsor, this instrument is to be signed by that person; if a partnership, by a partner for the partnership; if a corporation by a director of the company secretary of that corporation.

Specimen signature of appointee s22 [redacted]

Signature of witness

Date 09 / 07 / 2002

Company Seal - if a corporation, place an imprint of the Company Seal here.

- When this instrument is revoked the enterprise must advise the *Therapeutic Goods Administration* in writing of th date of the revocation.

Part 2 - Description of Data for Evaluation

Application types

- **Application to Register**

New Chemical or Biological Agent

1A new substance ☐

1B new salt or ester ☐

Other

2 new route of administration ☐

3 new combination ☐

5 Pharmaceutical Benefits Listing ☐

9 new strength ☐

10 new dosage form ☐

11 new generic product ☐

Indications

4A addition of new indication ☐

4B deletion of existing indication ☐

Other (continued)

12A formulation ☐

12I packaging ☐

12M other aspect of B1 data ☐

12N change to container ☐

- **Application to Vary Conditions**

Change in Pharmaceutical Data

12B specifications - raw material drug ☐

12C specifications - finished product ☐

12D specification - excipients ☐

12E synthetic route - raw material drug ☐

12F manufacturing procedure - finished product ☐

12G site of manufacture - raw material drug ☐

12H site of manufacture - finished product ☐

12I packaging ☐

12J additional pack size(s) in existing materials ☐

12K shelf life and/or storage conditions ☐

12L labelling ☐

12M other aspects of B1 data ☐

Other

2 new route of administration ☐

6 change in regulatory status ☐

7 change in dosage, dose regimen or maximum daily dose ☐

7A change in patient group ☐

13 not in 1 to 12 ☐

Change in Product Information

8A clinical aspects - safety related ☐

8B clinical aspects - non-safety related ☑

8C preclinical aspects (B2) ☐

8D pharmaceutical aspects (B1) ☐

8E other P1 ☐

Part 2 - Description of Data for Evaluation (*continued*)

If you consider you have not supplied such information as will allow the determination of the application, please attach a separate sheet detailing reasons.

Details of Data submitted

Section	Number of volumes	Number of pages	Number of copies
Pharmaceutical (B1)	-	-	-
Preclinical (B2)	-	-	-
Clinical (B3) Module 5	2	-	1
Summary (C) Module 1 Module 2	1 1	- -	4 4
Bioavailability			
Product information	In Module 1		
Other *(specify)*			

- Is this application in support of an application for pharmaceutical benefits listing? Yes ☐ No ☑

9 Relevant TGA file numbers/control numbers from previous correspondence

2004/07570	2005/1014/2		

9 Is the product in this application to replace an existing ARTG entry?

Yes ☐ No ☑

Current ARTG Registration No. of the existing entry *(see Guide)*

10 Export names

Do you intend to export this product using a different name from the registration name?

Yes ☐ No ☑ *If NO*, go to item **11**

State the export name(s) to be used for this product

Export name	1.
	2.
	3.
	4.
	5.

11 **Exchange of Evaluation Reports**

Do you give approval for exchange of evaluation reports with other regulatory agencies for this submission?

Yes ✓ No

Signature s22 [redacted]

Date 21 / 10 / 05
dd mm yy

Name *(please print)* s22 [redacted]

Position/Relationship to Sponsor [redacted]

Office Use Only

DEB

Control number

Application number

Part 3 - Drug Product Details

12 **Registration name (product name in Australia)** *(max 100 characters)*

INFANRIX HEXA injection composite pack (pre-filled syringe and vial)

13 **Code name**

16 **Relevant ARTG Registration number(s)**

1. 79078	2.	3.	4.

15 **Category of Therapeutic Goods** Goods included in this application:

Drugs only [ ] - Go to item **16**

Drug-Device combinations *(Drugs supplied in a therapeutic device)* [✓]

- attach a supplement for Therapeutic Devices form

Drugs supplied as a component of a therapeutic device kit [ ]

- attach a supplement for Therapeutic Devices form

Office Use Only

	Drug	Device
Defn	Y	N
Data	Y	
ADG		

Is a supplement for "Therapeutic Devices form" attached to this page? **Yes** [✓] **No** [ ]

18 **Pack Size and Poisons schedule**

Pack/container sizes in which this product is supplied	**SUSDP Schedule No. for this pack size** *(if not scheduled write "N")*
1. NO CHANGES	
2.	
3.	
4.	
5.	

Pin extra pages here

Therapeutic Device Supplement

Office Use Only
ARTG No.
ADG

1 **Category of Therapeutic Drug-Device Combination**

Products included in this application:

☑ Devices supplied in a drug – device combination - *complete Supplement part 1*

☐ Devices supplied as components of a therapeutic device kit, tray or pack - *complete Supplement part 2*

2 **Registration / Listing name**

INFANRIX HEXA injection composite pack (pre-filled syringe and vial)

NO CHANGES

Part 1

Device in a Drug - Device Combinations

Office Use Only

Individual device details

Attach a copy of Part 1 for each individual therapeutic device product included as part of a drug-device combination in the drug application.

1 **Product Name and/or Model Numbers**

BECTON-DICKINSON SCF SYRINGES 1mL AND SYRINGE ROUND FLANGE LUER LOK.

(max 250 characters)

Product No.

1 **Functional Description**

GLASS SYRINGE BARRELS, WITH OR WITHOUT ATTACHED NEEDLE. NEEDLE SIZE OF 23G1, 25G5/8, 25G1. RUBBER NEEDLE SHEILDS GREY BUTYL STOPPERS AND POLYSTYRENE PLUNGER RODS. THE ROUND FLANGE LUER SYRINGE HAS A POLYPROPYLENE BACKSTOP

ECRI - IMD Code

ECRI - IMD Code

Sterility Is this device, or any of its components, supplied sterile? Yes ☑ No ☐

Steam	☐ ST	Ethylene oxide	☑ EO	Filtration	☐ FT
Gamma irradiation	☑ GR	Dry heat	☐ DH	Other	☐

If OTHER, please specify (max 100 characters)

Source of Material Was material of human or other animal origin used in the manufacture and/or formulation of this device? Yes ☐ No ☑ Not applicable ☐ *(refer to Guide)*

specify types of animal origin

Office Use Only
Kit
N

Part 3 - Drug Product Details (*continued*)

Composite Packs Is this product a composite pack? Yes [✓] No [ ] *-If NO, go to "Dosage Form" details at Item* 18

- *If YES*, how many different drug components are there in this pack? 2

Note: complete a copy of items 18 to 21 and 23 to 29 for each type of drug component and pin the extra pages to this one.

- Description of this drug component *(maximum 50 characters)* NO CHANGES

Office use only

Dosage form NO CHANGES — Dosage Form code

19 Routes of administration

1. NO CHANGES — Admin. Route Code
2.
3.
4.

(max 150 characters)

20 Visual identification of dosage form NO CHANGES

21 Type of container in which this dosage form is to be supplied NO CHANGES — Container Code

(max 500 characters)

22 Proposed indications NO CHANGES

Part 3 - Drug Product Details *(continued)*

23 **Sterility** Is this product or any of its components, supplied sterile? **Yes** ☐ **No** ☐

Steam ☐ ST | Ethylene oxide ☐ EO | Filtration ☐ FT

Gamma irradiation ☐ GR | Dry heat ☐ DH | Other ☐ OT

If OTHER, please specify (max 100 characters)

24 **Proposed storage and shelf life**

- State the proposed temperature of storage of the product. *(Tick the appropriate box.)*

(i) Store below minus 18 degrees Celsius (deep freeze) ☐

(ii) Store below minus 5 degrees Celsius (freeze) ☐

(iii) Store below 8 degrees Celsius (refrigerate) ☐

(iv) Store at 2 to 8 degrees Celsius (refrigerate - do not freeze) ☐

(v) Store below 25 degrees Celsius ☐

(vi) Store below 30 degrees Celsius ☐

- State below whether any special additional storage precautions are necessary.

- State the proposed shelf life of the product. *(Tick the appropriate box)*

1 year ☐ 2 years ☐ 3 years ☐ 4 years ☐ 5 years ☐ Other *(please specify)* ☐

21 **Source of material** Was material of human or other animal origin used at any stage in the manufacture and/or formulation of these goods? **Yes** ☐ **No** ☐ **Not applicable** ☐

If YES, identify species

1. 2. 3.

Part 3 - Drug Product Details *(continued)*

26 Printed product material supplied*

(Tick one or more boxes as relevant.)

container label		CL
primary pack label		PP
package insert		IN
promotional material		PM
product information	✓	PI
other *(please specify)*	✓	OT

Product Information in Module 1.3.1.1
Consumer Medicine Information in Module 1.3.2

* Attach to this page.

Part 4 - Formulation details

27 Active Ingredients

Note: *Attach additional pages as required.*

Names used must be those published in the Australian Approved Names Lists, unless no appropriate name exists in the lists.

Office Use Only

Name NO CHANGES

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Office Use Only

Number of active ingredients *(including equivalence statements)* listed for this drug component *(last page only)*.

Part 4 - Formulation details *(continued)*

28 Excipients

Attach additional pages as required.

Names used must be those published in the Australian Approved Names Lists, unless no appropriate name exists in the lists.

Note: *List proprietary ingredients, the formulations of which have not been or will not be revealed to you by your supplier(s) on page 10.*

Office Use Only

Name NO CHANGES

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Office Use Only

Number of non-proprietary excipient ingredients listed for this drug component *(last page only)*.

Part 4 - Formulation details *(continued)*

29 **Proprietary Ingredients - the formulations of which have not been or will not be revealed by you by your supplier(s)**

Note: Attach additional pages as required.

(max 65 characters)

Office Use Only

Proprietary Ingredient name NO CHANGES

Name of supplier

Supplier's Enterprise Identification Code *(if known)*

Proprietary Ingredient ARTG number *(if known)*

Proprietary Ingredient name

Name of supplier

Supplier's Enterprise Identification Code *(if known)*

Proprietary Ingredient ARTG number *(if known)*

Proprietary Ingredient name

Name of supplier

Supplier's Enterprise Identification Code *(if known)*

Proprietary Ingredient ARTG number *(if known)*

Proprietary Ingredient name

Name of supplier

Supplier's Enterprise Identification Code *(if known)*

Proprietary Ingredient ARTG number *(if known)*

Proprietary Ingredient name

Name of supplier

Supplier's Enterprise Identification Code *(if known)*

Proprietary Ingredient ARTG number *(if known)*

- Number of Proprietary ingredients listed for this drug component
- How many completed "Enterprise Details" forms have you attached for proprietary ingredient suppliers?
- Have you requested the suppliers of proprietary ingredients to advise the Australian Register of Therapeutic Goods of the composition of the proprietary ingredient on a "Notification of a Proprietary Ingredient" form?

Yes ☐ No ☐

Part 5 - Manufacturer details

Principal Manufacturer's Details

Attach a copy of this section for each additional manufacturer.

33 **Principal manufacturer's business name** (max 100 characters) NO CHANGES

34 **Principal manufacturer's licence number** *(if applicable)*

32 **Principal manufacturer's enterprise identification code**

Office use only

Site Code

Alternative principal manufacturers

Note: Attach a copy of this section for each additional manufacturer.

33 **Alternative principal manufacturer's business name** (max 100 characters) NO CHANGES

34 **Alternative principal manufacturer's licence number** *(if applicable)*

35 **Alternative principal manufacturer's enterprise identification code**

Office use only

Site Code

Sub-manufacturers

Note: Attach a copy of this section for each additional sub-manufacturer.

34 **Sub-manufacturer's business name** (max 100 characters) NO CHANGES

37 **Sub-manufacture's licence number** *(if applicable)*

38 **Sub-manufacturer's enterprise identification code**

Office use only

Site Code

39 **Step in manufacture**

Part 6 - Overseas Manufacturer Details

40 Is evidence from a relevant overseas authority attached to establish that the principal manufacturer of the goods is of an acceptable standard?

N/A ☐ Yes ☐ No ☐ → *Attach separate sheet detailing reasons*

41 If documentation of the standard of the overseas manufacturer has previously been supplied as part of a successful application for registration or listing, state ARTG registration/listing number for the product here.

ARTG number

42 If acceptable documentation is not available, do you agree to pay the cost of an inspection of the principal overseas manufacturer by Australian inspectors if deemed necessary by the Secretary?

Yes ☐ No ☐ → *Attach separate sheet detailing reasons*

43 Has the overseas manufacturer agreed in writing to such an inspection?

Yes ☐ No ☐ → *Attach separate sheet detailing reasons*

Therapeutic Goods Act 1989

TGA Therapeutic Goods Administration

COMMONWEALTH DEPARTMENT OF HEALTH, HOUSING AND COMMUNITY SERVICES

Application – INFANRIX-HIB

(please tick the appropriate box)

☐ **for Registration (including Pharmaceutical Benefits Listing) of Drug Products**

☑ **to vary the Conditions of Registration of Drug Products**

(via Drug Evaluation Branch)

- To ensure this form is correctly completed, please refer to the explanatory guide issued for this application form before applying.
- Send **Original** of this form with a cheque for the appropriate fee(s) and an Enterprise Details form if necessary to:
  Note: Cheques should be made payable to: 'Therapeutic Goods Administration'.

via Courier

The Business Manager
Business Management Unit
Therapeutic Goods Administration
4th Floor, Alexander Building
Furzer Street
Phillip ACT
Australia

via Australia Post

The Business Manager
Business Management Unit
Therapeutic Goods Administration
PO Box 100
Woden ACT 2606
Australia

- Send a **copy** of this form with the Data for Evaluation to:

via Courier

The Director
Drug Evaluation Branch
5th Floor
Alexander Building
Furzer Street
Phillip ACT
Australia

via Australia Post

The Director
Drug Evaluation Branch
Therapeutic Goods Administration
PO Box 100
Woden ACT 2606
Australia

Part 1 - General Details

Sponsor details *(If an individual, provide full name; if a corporation, the registered company name under the Companies Code; or business names under which you propose to trade for the purposes of the Therapeutic Goods Act 1989.)*

1 **Sponsor's business name** *(max 100 characters)*

GLAXOSMITHKLINE AUSTRALIA PTY LTD

2 **Sponsor's enterprise identification code**

40010

3 **Enterprise details**

- Have you attached a completed "Enterprise Details" form? Yes ☐ No ☑

4 **Payment enclosed** *(for payment of relevant fees)*

$4,170.00

5 **Sponsor Application and Declaration**

- Sponsors should note that the *Therapeutic Goods Act 1989* provides penalties for making statements that are false or misleading in connection with an application for registration of therapeutic goods.

I apply to: *(delete whichever is not applicable)*

- ~~Register (including Pharmaceutical Benefits Listing)~~
- Vary the conditions of registration of

the goods described in this form and declare that the information given is, to the best of my knowledge, current and correct.

To the best of my knowledge, I certify that this application is accompanied by such information and in the required format as will allow the determination of the application (ie. complies with the current NDF guidelines for preparing applications to market drug products and any associated or supplementary guidelines). *(Refer to the Guide for details and Note on page 3 of this form.)*

Signature s22 [redacted]

Date 21 / 10 / 09
dd mm yy

Name *(please print)* s22 [redacted]

Position/ Relationship to Sponsor s22 [redacted]

If you are not the Sponsor, have you attached a copy of a current "Instrument of Appointment" authorising you to act as a duly appointed agent of the Sponsor. Yes ☑ No ☐

Office Use Only

Receipt number

Charge code

Fee $

Correct fee Yes ☐ No ☐

Enterprise ID

TGAIN

ARTG no.

Document 1

- Complete the authorisation below, or a copy, for each person you have appointed to submit applications for registration, listing or manufacturing licence on your behalf.
- Send the original authorisation to the *Therapeutic Goods Administration*. A copy of the authorisation should be included with each application (or group of applications) submitted by the authorised person on behalf of the enterprise.

Instrument of Appointment

- Please print full name where applicable.

I, s22 [redacted], GLAXOSMITHKLINE AUSTRALIA PTY LTD

being a sponsor or company director or company secretary of a sponsor of therapeutic goods in Australi

hereby appoint s22 [redacted]

as my/the sponsor's duly appointed agent to provide information and make declarations for the purpo of applications as required under the *Therapeutic Goods Act 1989*

Signature s22 [redacted]

Date 9 / 7 / '02

- Note: If an individual person is the sponsor, this instrument is to be signed by that person; if a partnership, b a partner for the partnership, if a corporation, by a director of the company secretary of that corporation

Specimen signature of appointee s22 [redacted]

Signature of witness [redacted]

Date 09 / 07 / 2002

Company Seal - if a corporation, place an imprint of the Company Seal here.

- When this instrument is revoked the enterprise must advise the *Therapeutic Goods Administration* in writing of it date of the revocation.

Part 2 - Description of Data for Evaluation

6 Application types

- **Application to Register**

New Chemical or Biological Agent

1A	new substance	☐
1B	new salt or ester	☐

Other

2	new route of administration	☐
3	new combination	☐
5	Pharmaceutical Benefits Listing	☐
9	new strength	☐
10	new dosage form	☐
11	new generic product	☐

Indications

4A	addition of new indication	☐
4B	deletion of existing indication	☐

Other (continued)

12A	formulation	☐
12I	packaging	☐
12M	other aspect of B1 data	☐
12N	change to container	☐

- **Application to Vary Conditions**

Change in Pharmaceutical Data

12B	specifications - raw material drug	☐
12C	specifications - finished product	☐
12D	specification - excipients	☐
12E	synthetic route - raw material drug	☐
12F	manufacturing procedure - finished product	☐
12G	site of manufacture - raw material drug	☐
12H	site of manufacture - finished product	☐
12I	packaging	☐
12J	additional pack size(s) in existing materials	☐
12K	shelf life and/or storage conditions	☐
12L	labelling	☐
12M	other aspects of B1 data	☐

Other

2	new route of administration	☐
6	change in regulatory status	☐
7	change in dosage, dose regimen or maximum daily dose	☐
7A	change in patient group	☐
13	not in 1 to 12	☐

Change in Product Information

8A	clinical aspects - safety related	☐
8B	clinical aspects - non-safety related	✓
8C	preclinical aspects (B2)	☐
8D	pharmaceutical aspects (B1)	☐
8E	other P1	☐

Part 2 - Description of Data for Evaluation (*continued*)

N : *If you consider you have not supplied such information as will allow the determination of the application, please attach a separate sheet detailing reasons.*

7 Details of Data submitted

Section	Number of volumes	Number of pages	Number of copies
Pharmaceutical (B1)	-	-	-
Preclinical (B2)	-	-	-
Clinical (B3) Module 5	2	-	1
Summary (C) Module 1	1	-	4
Module 2	1	-	4
Bioavailability			
Product information	In Module 1		
Other *(specify)*			

- Is this application in support of an application for pharmaceutical benefits listing? Yes ☐ No ☑

8 Relevant TGA file numbers/control numbers from previous correspondence

9 Is the product in this application to replace an existing ARTG entry?

Yes ☐ No ☑

Current ARTG Registration No. of the existing entry *(see Guide)*

10 Export names

Do you intend to export this product using a different name from the registration name?

Yes ☐ No ☑ *If NO*, go to item **11**

State the export name(s) to be used for this product

Export name

1.

2.

3.

4.

5.

Exchange of Evaluation Reports

Do you give approval for exchange of evaluation reports with other regulatory agencies for this submission?

Yes ✓ No

Signature [s22 redacted]

Date 21 / 10 / 05
dd mm yy

Name *(please print)* [s22 redacted]

Position/Relationship to Sponsor [s22 redacted]

Office Use Only

DEB

Control number

Application number

Part 3 - Drug Product Details

33 **Registration name (product name in Australia)** *(max 100 characters)*

INFANRIX-HIB injection vial composite pack

INFANRIX-HIB injection syringe composite pack

13 **Code name**

10 **Relevant ARTG Registration number(s)**

1.	2.	3.	4.
67737	67738		

15 **Category of Therapeutic Goods** Goods included in this application:

Drugs only [ ] - Go to item 16

Drug-Device combinations *(Drugs supplied in a therapeutic device)* [✓]

- attach a supplement for Therapeutic Devices form

Drugs supplied as a component of a therapeutic device kit [ ]

- attach a supplement for Therapeutic Devices form

Office Use Only

	Drug	Device
Defn	Y	N
Data	Y	
ADG		

Is a supplement for "Therapeutic Devices form" attached to this page? **Yes** [✓] **No** [ ]

13 **Pack Size and Poisons schedule**

Pack/container sizes in which this product is supplied	**SUSDP Schedule No. for this pack size** *(if not scheduled write "N")*
1. NO CHANGES	
2.	
3.	
4.	
5.	

Pin extra pages here

Document 1

Therapeutic Device Supplement

Office Use Only

ARTG No.

ADG

1 Category of Therapeutic Drug-Device Combination

Products included in this application:

☑ Devices supplied in a drug – device combination - *complete Supplement part 1*

☐ Devices supplied as components of a therapeutic device kit, tray or pack - *complete Supplement part 2*

2 Registration / Listing name

INFANRIX-HIB injection syringe composite pack

NO CHANGES

Part 1

Device in a Drug - Device Combinations

Office Use Only

Individual device details

Attach a copy of Part 1 for each individual therapeutic device product included as part of a drug-device combination in the drug application.

1 Product Name and/or Model Numbers

BECTON-DICKINSON SCF SYRINGES 1mL AND SYRINGE ROUND FLANGE LUER LOK.

(max 250 characters)

Product No.

Functional Description

GLASS SYRINGE BARRELS, WITH OR WITHOUT ATTACHED NEEDLE. NEEDLE SIZE OF 23G1, 25G5/8, 25G1. RUBBER NEEDLE SHIELDS GREY BUTYL STOPPERS AND POLYSTYRENE PLUNGER RODS. THE ROUND FLANGE LUER SYRINGE HAS A POLYPROPYLENE BACKSTOP

ECRI - IMD Code

ECRI - IMD Code

Sterility

Is this device, or any of its components, supplied sterile?

Yes ☑ No ☐

Steam ☐ ST

Ethylene oxide ☑ EO

Filtration ☐ FT

Gamma irradiation ☑ GR

Dry heat ☐ DH

Other ☐

If OTHER, please specify (max 100 characters)

Source of Material

Was material of human or other animal origin used in the manufacture and/or formulation of this device?

Yes ☐ No ☑ Not applicable ☐ *(refer to Guide)*

specify types of animal origin

Office Use Only

Kit

N

Part 3 - Drug Product Details (*continued*)

1. **Composite Packs** Is this product a composite pack? Yes [✓] No [ ] *-If NO, go to "Dosage Form" details at item* **18**

- *If YES,* how many different drug components are there in this pack? [2]

Note: complete a copy of items 18 to 21 and 23 to 29 for each type of drug component and pin the extra pages to this one.

- Description of this drug component *(maximum 50 characters)*

NO CHANGES

Office use only

Dosage form NO CHANGES — Dosage Form code

10 **Routes of administration**

1. NO CHANGES — Admin. Route Code
2.
3.
4.

26 **Visual identification of dosage form** *(max 150 characters)*

NO CHANGES

21 **Type of container in which this dosage form is to be supplied**

NO CHANGES — Container Code

21 **Proposed indications** *(max 500 characters)*

NO CHANGES

Part 3 - Drug Product Details *(continued)*

23 **Sterility** Is this product or any of its components, supplied sterile? **Yes** ☐ **No** ☐

Steam ☐ ST | Ethylene oxide ☐ EO | Filtration ☐ FT

Gamma irradiation ☐ GR | Dry heat ☐ DH | Other ☐ OT

If OTHER, please specify (max 100 characters)

24 **Proposed storage and shelf life**

- State the proposed temperature of storage of the product. *(Tick the appropriate box.)*

(i) Store below minus 18 degrees Celsius (deep freeze) ☐

(ii) Store below minus 5 degrees Celsius (freeze) ☐

(iii) Store below 8 degrees Celsius (refrigerate) ☐

(iv) Store at 2 to 8 degrees Celsius (refrigerate - do not freeze) ☐

(v) Store below 25 degrees Celsius ☐

(vi) Store below 30 degrees Celsius ☐

- State below whether any special additional storage precautions are necessary.

- State the proposed shelf life of the product. *(Tick the appropriate box)*

1 year ☐ 2 years ☐ 3 years ☐ 4 years ☐ 5 years ☐ Other *(please specify)* ☐

t

10 **Source of material** Was material of human or other animal origin used at any stage in the manufacture and/or formulation of these goods? **Yes** ☐ **No** ☐ **Not applicable** ☐

If YES, identify species

1. 2. 3.

Part 3 - Drug Product Details *(continued)*

26 **Printed product material supplied***

(Tick one or more boxes as relevant.)

container label		CL
primary pack label		PP
package insert		IN
promotional material		PM
product information	✓	PI
other *(please specify)*	✓	OT

Product Information in Module 1.3.1.1
Consumer Medicine Information in Module 1.3.2

* Attach to this page.

Part 4 - Formulation details

27 Active Ingredients

Note: *Attach additional pages as required.*

Names used must be those published in the Australian Approved Names Lists, unless no appropriate name exists in the lists.

Office Use Only

Name NO CHANGES

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Office Use Only

Number of active ingredients *(including equivalence statements)* listed for this drug component *(last page only)*.

Part 4 - Formulation details *(continued)*

28 Excipients

Attach additional pages as required.

Names used must be those published in the Australian Approved Names Lists, unless no appropriate name exists in the lists

Note: *List proprietary ingredients, the formulations of which have not been or will not be revealed to you by your supplier(s) on page 10.*

Office Use Only

Name NO CHANGES

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Office Use Only

Number of non-proprietary excipient ingredients listed for this drug component *(last page only)*.

Part 4 - Formulation details *(continued)*

29 **Proprietary Ingredients - the formulations of which have not been or will not be revealed by you by your supplier(s)**

Note: *Attach additional pages as required.*

(max 65 characters)

Office Use Only

Proprietary Ingredient name NO CHANGES

Name of supplier

Supplier's Enterprise Identification Code *(if known)*

Proprietary Ingredient ARTG number *(if known)*

Proprietary Ingredient name

Name of supplier

pplier's Enterprise Identification Code *(if known)*

Proprietary Ingredient ARTG number *(if known)*

Proprietary Ingredient name

Name of supplier

Supplier's Enterprise Identification Code *(if known)*

Proprietary Ingredient ARTG number *(if known)*

Proprietary Ingredient name

Name of supplier

Supplier's Enterprise Identification Code *(if known)*

Proprietary Ingredient ARTG number *(if known)*

Proprietary Ingredient name

Name of supplier

Supplier's Enterprise Identification Code *(if known)*

Proprietary Ingredient ARTG number *(if known)*

- Number of Proprietary ingredients listed for this drug component

- How many completed "Enterprise Details" forms have you attached for proprietary ingredient suppliers?

- Have you requested the suppliers of proprietary ingredients to advise the Australian Register of Therapeutic Goods of the composition of the proprietary ingredient on a "Notification of a Proprietary Ingredient" form?

Yes [ ] No [ ]

Part 5 - Manufacturer details

Principal Manufacturer's Details

Note: Attach a copy of this section for each additional manufacturer.

30 **Principal manufacturer's business name** *(max 100 characters)* NO CHANGES

21 **Principal manufacturer's licence number** *(if applicable)*

32 **Principal manufacturer's enterprise identification code**

Office use only

Site Code

Alternative principal manufacturers

Note: Attach a copy of this section for each additional manufacturer.

34 **Alternative principal manufacturer's business name** *(max 100 characters)* NO CHANGES

36 **Alternative principal manufacturer's licence number** *(if applicable)*

35 **Alternative principal manufacturer's enterprise identification code**

Office use only

Site Code

Sub-manufacturers

Note: Attach a copy of this section for each additional sub-manufacturer.

33 **Sub-manufacturer's business name** *(max 100 characters)* NO CHANGES

37 **Sub-manufacture's licence number** *(if applicable)*

Office use only

Site Code

38 **Sub-manufacturer's enterprise identification code**

39 **Step in manufacture**

Part 8 - Overseas Manufacturer Details

40 Is evidence from a relevant overseas authority attached to establish that the principal manufacturer of the goods is of an acceptable standard?

N/A ☐ Yes ☐ No ☐ → *Attach separate sheet detailing reasons*

41 If documentation of the standard of the overseas manufacturer has previously been supplied as part of a successful application for registration or listing, state ARTG registration/listing number for the product here.

ARTG number ☐

42 If acceptable documentation is not available, do you agree to pay the cost of an inspection of the principal overseas manufacturer by Australian inspectors if deemed necessary by the Secretary?

Yes ☐ No ☐ → *Attach separate sheet detailing reasons*

43 Has the overseas manufacturer agreed in writing to such an inspection?

Yes ☐ No ☐ → *Attach separate sheet detailing reasons*

Therapeutic Goods Act 1989

TGA Therapeutic Goods Administration

COMMONWEALTH DEPARTMENT OF HEALTH, HOUSING AND COMMUNITY SERVICES

Application – INFANRIX PENTA

(please tick the appropriate box)

☐ **for Registration (including Pharmaceutical Benefits Listing) of Drug Products**

☑ **to vary the Conditions of Registration of Drug Products**

(via Drug Evaluation Branch)

- To ensure this form is correctly completed, please refer to the explanatory guide issued for this application form before applying.
- Send **Original** of this form with a cheque for the appropriate fee(s) and an Enterprise Details form if necessary to:
  Note: Cheques should be made payable to: 'Therapeutic Goods Administration'.

via Courier

The Business Manager
Business Management Unit
Therapeutic Goods Administration
4th Floor, Alexander Building
Furzer Street
Phillip ACT
Australia

via Australia Post

The Business Manager
Business Management Unit
Therapeutic Goods Administration
PO Box 100
Woden ACT 2606
Australia

- Send a **copy** of this form with the Data for Evaluation to:

via Courier

The Director
Drug Evaluation Branch
5th Floor
Alexander Building
Furzer Street
Phillip ACT
Australia

via Australia Post

The Director
Drug Evaluation Branch
Therapeutic Goods Administration
PO Box 100
Woden ACT 2606
Australia

Part 1 - General Details

Sponsor details *(If an individual, provide full name; if a corporation, the registered company name under the Companies Code; or business names under which you propose to trade for the purposes of the Therapeutic Goods Act 1989.)*

1 **Sponsor's business name** *(max 100 characters)*

GLAXOSMITHKLINE AUSTRALIA PTY LTD

2 **Sponsor's enterprise identification code**

40010

3 **Enterprise details**

- Have you attached a completed "Enterprise Details" form? Yes ☐ No ☑

4 **Payment enclosed** *(for payment of relevant fees)*

$4,170.00

5 **Sponsor Application and Declaration**

- Sponsors should note that the *Therapeutic Goods Act 1989* provides penalties for making statements that are false or misleading in connection with an application for registration of therapeutic goods.

I apply to: *(delete whichever is not applicable)*

- ~~Register (including Pharmaceutical Benefits Listing)~~
- Vary the conditions of registration of

the goods described in this form and declare that the information given is, to the best of my knowledge, current and correct.

To the best of my knowledge, I certify that this application is accompanied by such information and in the required formal as will allow the determination of the application (ie. complies with the current NDF guidelines for preparing applications to market drug products and any associated or supplementary guidelines). *(Refer to the Guide for details and Note on page 3 of this form)*

Signature s22 [redacted]

Date 21 / 10 / 05 (dd / mm / yy)

Name *(please print)* s22 [redacted]

Position/ Relationship to Sponsor s22 [redacted]

If you are not the Sponsor, have you attached a copy of a current "Instrument of Appointment" authorising you to act as a duly appointed agent of the Sponsor. Yes ☑ No ☐

Office Use Only

Receipt number

Charge code

Fee $

Correct fee Yes ☐ No ☐

Enterprise ID

TGAIN

ARTG no.

Document 1

8 • Complete the authorisation below, or a copy, for each person you have appointed to submit applications for registration, listing or manufacturing licence on your behalf.

• Send the original authorisation to the *Therapeutic Goods Administration*. A copy of the authorisation should be included with each application (or group of applications) submitted by the authorised person on behalf of the enterprise.

Instrument of Appointment

• Please print full name where applicable.

I, s22 [redacted], GLAXOSMITHKLINE AUSTRALIA PTY LTD

being a sponsor or company director or company secretary of a sponsor of therapeutic goods in Australi

hereby appoint s22 [redacted]

as my/the sponsor's duly appointed agent to provide information and make declarations for the purpo of applications as required under the *Therapeutic Goods Act 1989*.

Signature s22 [redacted]

Date 9 / 7 / '02

• Note: If an individual person is the sponsor, this instrument is to be signed by that person; if a partnership, b a partner for the partnership, if a corporation, by a director of the company secretary of that corporation

Specimen signature of appointee s22 [redacted]

Signature of witness [redacted]

Date 09 / 07 / 2002

Company Seal - if a corporation, place an imprint of the Company Seal here.

• When this instrument is revoked the enterprise must advise the *Therapeutic Goods Administration* in writing of th date of the revocation.

Part 2 - Description of Data for Evaluation

6 Application types

- **Application to Register**

New Chemical or Biological Agent

1A new substance ☐

1B new salt or ester ☐

Other

2 new route of administration ☐

3 new combination ☐

5 Pharmaceutical Benefits Listing ☐

9 new strength ☐

10 new dosage form ☐

11 new generic product ☐

Indications

4A addition of new indication ☐

4B deletion of existing indication ☐

Other (continued)

12A formulation ☐

12I packaging ☐

12M other aspect of B1 data ☐

12N change to container ☐

- **Application to Vary Conditions**

Change in Pharmaceutical Data

12B specifications - raw material drug ☐

12C specifications - finished product ☐

12D specification - excipients ☐

12E synthetic route - raw material drug ☐

12F manufacturing procedure - finished product ☐

12G site of manufacture - raw material drug ☐

12H site of manufacture - finished product ☐

12I packaging ☐

12J additional pack size(s) in existing materials ☐

12K shelf life and/or storage conditions ☐

12L labelling ☐

12M other aspects of B1 data ☐

Other

2 new route of administration ☐

6 change in regulatory status ☐

7 change in dosage, dose regimen or maximum daily dose ☐

7A change in patient group ☐

13 not in 1 to 12 ☐

Change in Product Information

8A clinical aspects - safety related ☐

8B clinical aspects - non-safety related ☑

8C preclinical aspects (B2) ☐

8D pharmaceutical aspects (B1) ☐

8E other P1 ☐

Part 2 - Description of Data for Evaluation *(continued)*

N *If you consider you have not supplied such information as will allow the determination of the application, please attach a separate sheet detailing reasons.*

7 Details of Data submitted

Section	Number of volumes	Number of pages	Number of copies
Pharmaceutical (B1)	-	-	-
Preclinical (B2)	-	-	-
Clinical (B3) Module 5	2	-	1
Summary (C) Module 1	1	-	4
Module 2	1	-	4
Bioavailability			
Product information	In Module 1		
Other *(specify)*			

- Is this application in support of an application for pharmaceutical benefits listing? Yes ☐ No ☑

8 Relevant TGA file numbers/control numbers from previous correspondence

2004/07570	2005/1014/2		

8 Is the product in this application to replace an existing ARTG entry?

Yes ☐ No ☑

Current ARTG Registration No. of the existing entry *(see Guide)*

8 Export names

Do you intend to export this product using a different name from the registration name?

Yes ☐ No ☑ *If NO*, go to item **11**

State the export name(s) to be used for this product

Export name

1.

2.

3.

4.

5.

11 **Exchange of Evaluation Reports**

Do you give approval for exchange of evaluation reports with other regulatory agencies for this submission? **Yes** ✓ **No** ☐

Signature s22 [redacted]

Date 21 / 10 / 05
dd mm yy

Name *(please print)* s22 [redacted]

Position/Relationship to Sponsor [redacted]

Office Use Only

DEB

Control number

Application number

Part 3 - Drug Product Details

12 **Registration name (product name in Australia)** *(max 100 characters)*

INFANRIX PENTA 0.5mL injection vial

INFANRIX PENTA 0.5mL injection syringe

13 **Code name**

10 **Relevant ARTG Registration number(s)**

1.	2.	3.	4.
79991	79079		

15 **Category of Therapeutic Goods** Goods included in this application:

Drugs only [ ] - Go to item **16**

Drug-Device combinations *(Drugs supplied in a therapeutic device)* [✓]

- attach a supplement for Therapeutic Devices form

Drugs supplied as a component of a therapeutic device kit [ ]

- attach a supplement for Therapeutic Devices form

Office Use Only

	Drug	Device
Defn	Y	N
Data	Y	
ADG		

Is a supplement for "Therapeutic Devices form" attached to this page? Yes [✓] No [ ]

16 **Pack Size and Poisons schedule**

Pack/container sizes in which this product is supplied	**SUSDP Schedule No. for this pack size** *(if not scheduled write "N")*
1. NO CHANGES	
2.	
3.	
4.	
5.	

Pin extra pages here

Therapeutic Device Supplement

Office Use Only
ARTG No.
ADG

1 **Category of Therapeutic Drug-Device Combination**

Products included in this application:

☑ Devices supplied in a drug – device combination - *complete Supplement part 1*

☐ Devices supplied as components of a therapeutic device kit, tray or pack - *complete Supplement part 2*

2 **Registration / Listing name**

INFANRIX PENTA 0·5mL injection syringe

Part 1

Device in a Drug - Device Combinations

Office Use Only

Individual device details

Attach a copy of Part 1 for each individual therapeutic device product included as part of the drug-device combination in the drug application.

1 **Product Name and/or Model Numbers**

BECTON-DICKINSON SCF SYRINGES 1mL AND SYRINGE ROUND FLANGE LUER LOK.

Product No.

(max 250 characters)

2 **Functional Description**

GLASS SYRINGE BARRELS, WITH OR WITHOUT ATTACHED NEEDLE, NEEDLE SIZE OF 23GL, 25GS/S, 25GL. RUBBER NEEDLE SHEILDS GREY BUTYL STOPPERS AND POLYSTYRENE PLUNGER RODS. THE ROUND FLANGE LUER SYRINGE HAS A POLYPROPYLENE BACKSTOP

ECRI - IMD Code

3 **ECRI - IMD Code**

ECRI - IMD Code

4 **Sterility**

Is this device, or any of its components, supplied sterile? Yes ☑ No ☐

Steam ☐ ST
Ethylene oxide ☑ EO
Filtration ☐ FT
Gamma irradiation ☑ GR
Dry heat ☐ DH
Other ☐

If OTHER, *please specify (max 100 characters)*

5 **Source of Material**

Was material of human or other animal origin used in the manufacture and/or formulation of this device? Yes ☐ No ☑ Not applicable ☐ *(refer to Guide)*

specify types of animal origin

Office Use Only
Kit
N

Part 3 - Drug Product Details (*continued*)

1. **Composite Packs** Is this product a composite pack? Yes ☐ No ☑ *-If NO, go to "Dosage Form" details at item* **18**

- ***If YES,*** how many different drug components are there in this pack? ☐

  Note: complete a copy of items 18 to 21 and 23 to 29 for each type of drug component and pin the extra pages to this one.

- Description of this drug component
  (maximum 50 characters)

Office use only

18 **Dosage form** NO CHANGES — Dosage Form code

19 **Routes of administration**
1. NO CHANGES — Admin. Route Code
2.
3.
4.

(max 150 characters)

20 **Visual identification of dosage form** NO CHANGES

21 **Type of container in which this dosage form is to be supplied** NO CHANGES — Container Code

(max 500 characters)

21 **Proposed indications** NO CHANGES

Part 3 - Drug Product Details *(continued)*

23 **Sterility** Is this product or any of its components, supplied sterile? **Yes** ☐ **No** ☐

Steam ☐ ST | Ethylene oxide ☐ EO | Filtration ☐ FT

Gamma irradiation ☐ GR | Dry heat ☐ DH | Other ☐ OT

If OTHER, please specify (max 100 characters)

24 **Proposed storage and shelf life**

- State the proposed temperature of storage of the product. *(Tick the appropriate box.)*

(i) Store below minus 18 degrees Celsius (deep freeze) ☐

(ii) Store below minus 5 degrees Celsius (freeze) ☐

(iii) Store below 8 degrees Celsius (refrigerate) ☐

(iv) Store at 2 to 8 degrees Celsius (refrigerate - do not freeze) ☐

(v) Store below 25 degrees Celsius ☐

(vi) Store below 30 degrees Celsius ☐

- State below whether any special additional storage precautions are necessary.

- State the proposed shelf life of the product. *(Tick the appropriate box)*

1 year ☐ 2 years ☐ 3 years ☐ 4 years ☐ 5 years ☐ Other *(please specify)* ☐

t

25 **Source of material** Was material of human or other animal origin used at any stage in the manufacture and/or formulation of these goods? **Yes** ☐ **No** ☐ **Not applicable** ☐

If YES, identify species

1. 2. 3.

Part 3 - Drug Product Details *(continued)*

26 Printed product material supplied*

(Tick one or more boxes as relevant.)

container label		CL
primary pack label		PP
package insert		IN
promotional material		PM
product information	✓	PI
other *(please specify)*	✓	OT

t

Product Information in Module 1.3.1.1
Consumer Medicine Information in Module 1.3.2

* Attach to this page.

Part 4 - Formulation details

27 Active Ingredients

Note: *Attach additional pages as required.*

Names used must be those published in the Australian Approved Names Lists, unless no appropriate name exists in the lists.

			Office Use Only
Name	NO CHANGES		
Quantity		Units	
Name			
Quantity		Units	
Name			
Quantity		Units	
Name			
Quantity		Units	
Name			
Quantity		Units	
Name			
Quantity		Units	
Name			
Quantity		Units	
Name			
Quantity		Units	
Name			
Quantity		Units	

Office Use Only

Number of active ingredients *(including equivalence statements)* listed for this drug component *(last page only)*.

Part 4 - Formulation details *(continued)*

28 Excipients

Attach additional pages as required.

Names used must be those published in the Australian Approved Names Lists, unless no appropriate name exists in the lists.

Note: *List proprietary ingredients, the formulations of which have not been or will not be revealed to you by your supplier(s) on page 10.*

Office Use Only

Name NO CHANGES

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Office Use Only

Number of non-proprietary excipient ingredients listed for this drug component *(last page only)*.

Part 4 - Formulation details *(continued)*

29 **Proprietary Ingredients - the formulations of which have not been or will not be revealed by you by your supplier(s)**

Note: *Attach additional pages as required.*

(max 65 characters)

Office Use Only

Proprietary Ingredient name NO CHANGES

Name of supplier

Supplier's Enterprise Identification Code *(if known)*

Proprietary Ingredient ARTG number *(if known)*

Proprietary Ingredient name

Name of supplier

pplier's Enterprise Identification Code *(if known)*

Proprietary Ingredient ARTG number *(if known)*

Proprietary Ingredient name

Name of supplier

Supplier's Enterprise Identification Code *(if known)*

Proprietary Ingredient ARTG number *(if known)*

Proprietary Ingredient name

Name of supplier

Supplier's Enterprise Identification Code *(if known)*

Proprietary Ingredient ARTG number *(if known)*

Proprietary Ingredient name

Name of supplier

Supplier's Enterprise Identification Code *(if known)*

Proprietary Ingredient ARTG number *(if known)*

- Number of Proprietary ingredients listed for this drug component
- How many completed "Enterprise Details" forms have you attached for proprietary ingredient suppliers?
- Have you requested the suppliers of proprietary ingredients to advise the Australian Register of Therapeutic Goods of the composition of the proprietary Ingredient on a "Notification of a Proprietary Ingredient" form?

Yes ☐ No ☐

Part 5 - Manufacturer details

Principal Manufacturer's Details

Note: Attach a copy of this section for each additional manufacturer.

33 **Principal manufacturer's business name** *(max 100 characters)* NO CHANGES

34 **Principal manufacturer's licence number** *(if applicable)*

32 **Principal manufacturer's enterprise identification code**

Office use only Site Code

Alternative principal manufacturers

Note: Attach a copy of this section for each additional manufacturer.

33 **Alternative principal manufacturer's business name** *(max 100 characters)* NO CHANGES

33 **Alternative principal manufacturer's licence number** *(if applicable)*

35 **Alternative principal manufacturer's enterprise identification code**

Office use only Site Code

Sub-manufacturers

Note: Attach a copy of this section for each additional sub-manufacturer.

36 **Sub-manufacturer's business name** *(max 100 characters)* NO CHANGES

37 **Sub-manufacture's licence number** *(if applicable)*

Office use only Site Code

38 **Sub-manufacturer's enterprise identification code**

39 **Step in manufacture**

Part 6 - Overseas Manufacturer Details

40 Is evidence from a relevant overseas authority attached to establish that the principal manufacturer of the goods is of an acceptable standard?

N/A ☐ Yes ☐ No ☐ → *Attach separate sheet detailing reasons*

41 If documentation of the standard of the overseas manufacturer has previously been supplied as part of a successful application for registration or listing, state ARTG registration/listing number for the product here.

ARTG number

42 If acceptable documentation is not available, do you agree to pay the cost of an inspection of the principal overseas manufacturer by Australian inspectors if deemed necessary by the Secretary?

Yes ☐ No ☐ → *Attach separate sheet detailing reasons*

43 Has the overseas manufacturer agreed in writing to such an inspection?

Yes ☐ No ☐ → *Attach separate sheet detailing reasons*

Therapeutic Goods Act 1989

TGA Therapeutic Goods Administration

COMMONWEALTH DEPARTMENT OF HEALTH, HOUSING AND COMMUNITY SERVICES

Application – INFANRIX-IPV

(please tick the appropriate box)

☐ **for Registration (including Pharmaceutical Benefits Listing) of Drug Products**

☑ **to vary the Conditions of Registration of Drug Products**

(via Drug Evaluation Branch)

- To ensure this form is correctly completed, please refer to the explanatory guide issued for this application form before applying.
- Send **Original** of this form with a cheque for the appropriate fee(s) and an Enterprise Details form if necessary to:
  Note: Cheques should be made payable to: 'Therapeutic Goods Administration'.

via Courier

The Business Manager
Business Management Unit
Therapeutic Goods Administration
4th Floor, Alexander Building
Furzer Street
Phillip ACT
Australia

via Australia Post

The Business Manager
Business Management Unit
Therapeutic Goods Administration
PO Box 100
Woden ACT 2606
Australia

- Send a **copy** of this form with the Data for Evaluation to:

via Courier

The Director
Drug Evaluation Branch
5th Floor
Alexander Building
Furzer Street
Phillip ACT
Australia

via Australia Post

The Director
Drug Evaluation Branch
Therapeutic Goods Administration
PO Box 100
Woden ACT 2606
Australia

Part 1 - General Details

Sponsor details *(If an individual, provide full name; if a corporation, the registered company name under the Companies Code; or business names under which you propose to trade for the purposes of the Therapeutic Goods Act 1989.)*

Sponsor's business name *(max 100 characters)*

GLAXOSMITHKLINE AUSTRALIA PTY LTD

Sponsor's enterprise identification code

400.0

Enterprise details

- Have you attached a completed "Enterprise Details" form? Yes ☐ No ☑

Payment enclosed *(for payment of relevant fees)* $4,170.00

5 Sponsor Application and Declaration

- Sponsors should note that the *Therapeutic Goods Act 1989* provides penalties for making statements that are false or misleading in connection with an application for registration of therapeutic goods.

I apply to: *(delete whichever is not applicable)*

- ~~Register (including Pharmaceutical Benefits Listing)~~
- Vary the conditions of registration of

the goods described in this form and declare that the information given is, to the best of my knowledge, current and correct.

To the best of my knowledge, I certify that this application is accompanied by such information and in the required format as will allow the determination of the application (ie. complies with the current NDF guidelines for preparing applications to market drug products and any associated or supplementary guidelines). *(Refer to the Guide for details and Note on page 3 of this form.)*

Signature s22 [redacted]

Date 21 / 10 / 05 (dd / mm / yy)

Name *(please print)* s22 [redacted]

Position/ Relationship to Sponsor [redacted]

If you are not the Sponsor, have you attached a copy of a current "Instrument of Appointment" authorising you to act as a duly appointed agent of the Sponsor. Yes ☑ No ☐

Office Use Only

Receipt number

Charge code

Fee $

Correct fee Yes ☐ No ☐

Enterprise ID

TGAIN

ARTG no.

Document 1

8 • Complete the authorisation below, or a copy, for each person you have appointed to submit applications for registration, listing or manufacturing licence on your behalf.

• Send the original authorisation to the *Therapeutic Goods Administration*. A copy of the authorisation should be included with each application (or group of applications) submitted by the authorised person on behalf of the enterprise.

Instrument of Appointment

• Please print full name where applicable.

I, s22 [redacted] GLAXOSMITHKLINE AUSTRALIA PTY LTD

being a sponsor or company director or company secretary of a sponsor of therapeutic goods in Australi

hereby appoint s22 [redacted]

as my/the sponsor's duly appointed agent to provide information and make declarations for the purpo of applications as required under the *Therapeutic Goods Act 1989*.

Signature s22 [redacted]

Date 9 / 7 / '02

• Note: If an individual person is the sponsor, this instrument is to be signed by that person. If a partnership, b a partner for the partnership, if a corporation, by a director of the company secretary of that corporation

Specimen signature of appointee s22 [redacted]

Signature of witness

Date 09 / 07 / 2002

Company Seal - if a corporation, place an imprint of the Company Seal here.

• When this instrument is revoked the enterprise must advise the *Therapeutic Goods Administration* in writing of th date of the revocation

Part 2 - Description of Data for Evaluation

6 Application types

- **Application to Register**

New Chemical or Biological Agent

1A new substance ☐

1B new salt or ester ☐

Other

2 new route of administration ☐

3 new combination ☐

5 Pharmaceutical Benefits Listing ☐

9 new strength ☐

10 new dosage form ☐

11 new generic product ☐

Indications

4A addition of new indication ☐

4B deletion of existing indication ☐

Other (continued)

12A formulation ☐

12I packaging ☐

12M other aspect of B1 data ☐

12N change to container ☐

- **Application to Vary Conditions**

Change in Pharmaceutical Data

12B specifications - raw material drug ☐

12C specifications - finished product ☐

12D specification - excipients ☐

12E synthetic route - raw material drug ☐

12F manufacturing procedure - finished product ☐

12G site of manufacture - raw material drug ☐

12H site of manufacture - finished product ☐

12I packaging ☐

12J additional pack size(s) in existing materials ☐

12K shelf life and/or storage conditions ☐

12L labelling ☐

12M other aspects of B1 data ☐

Other

2 new route of administration ☐

6 change in regulatory status ☐

7 change in dosage, dose regimen or maximum daily dose ☐

7A change in patient group ☐

13 not in 1 to 12 ☐

Change in Product Information

8A clinical aspects - safety related ☐

8B clinical aspects - non-safety related ☑

8C preclinical aspects (B2) ☐

8D pharmaceutical aspects (B1) ☐

8E other P1 ☐

Part 2 - Description of Data for Evaluation (*continued*)

If you consider you have not supplied such information as will allow the determination of the application, please attach a separate sheet detailing reasons.

7 Details of Data submitted

Section	Number of volumes	Number of pages	Number of copies
Pharmaceutical (B1)	-	-	-
Preclinical (B2)	-	-	-
Clinical (B3) Module 5	2	-	1
Summary (C) Module 1	1	-	4
Module 2	1	-	4
Bioavailability			
Product information	In Module 1		
Other (specify)			

- Is this application in support of an application for pharmaceutical benefits listing? Yes ☐ No ☑

8 Relevant TGA file numbers/control numbers from previous correspondence

9 Is the product in this application to replace an existing ARTG entry?

Yes ☐ No ☑

Current ARTG Registration No. of the existing entry *(see Guide)*

10 Export names

Do you intend to export this product using a different name from the registration name?

Yes ☐ No ☑ *If NO, go to item* **11**

State the export name(s) to be used for this product

Export name	1.
	2.
	3.
	4.
	5.

11 **Exchange of Evaluation Reports**

Do you give approval for exchange of evaluation reports with other regulatory agencies for this submission? **Yes** ✓ **No**

Signature s22 [redacted]

Date 21 / 10 / 05
dd mm yy

Name (please print) s22 [redacted]

Position/Relationship to Sponsor [redacted]

Office Use Only

DEB

Control number

Application number

Part 3 - Drug Product Details

33	Registration name (product name in Australia) *(max 100 characters)*	INFANRIX-IPV 0.5mL injection vial INFANRIX-IPV 0.5mL injection syringe
13	Code name	
16	Relevant ARTG Registration number(s)	1. 80848 | 2. 80847 | 3. | 4.

15 Category of Therapeutic Goods — Goods included in this application:

- **Drugs only** [ ] - Go to item **16**
- **Drug-Device combinations** *(Drugs supplied in a therapeutic device)* [✓]
  - attach a supplement for Therapeutic Devices form
- **Drugs supplied as a component of a therapeutic device kit** [ ]
  - attach a supplement for Therapeutic Devices form

Office Use Only

	Drug	Device
Defn	Y	N
Data	Y	
ADG		

Is a supplement for "Therapeutic Devices form" attached to this page? **Yes** [✓] **No** [ ]

16 Pack Size and Poisons schedule

Pack/container sizes in which this product is supplied	**SUSDP Schedule No. for this pack size** *(if not scheduled write "N")*
1. NO CHANGES	
2.	
3.	
4.	
5.	

Pin extra pages here

Therapeutic Device Supplement

Office Use Only
ARTG No.
ADG

1 **Category of Therapeutic Drug-Device Combination**

Products included in this application:

☑ Devices supplied in a drug – device combination - *complete Supplement part 1*

☐ Devices supplied as components of a therapeutic device kit, tray or pack - *complete Supplement part 2*

2 **Registration / Listing name**

INFANRIX - IPV 0.5mL injection syringe

NO CHANGES

Device in a Drug - Device Combinations

Part 1

Office Use Only

Individual device details

Attach a copy of Part 1 for each individual therapeutic device product included as part of a drug-device combination in the drug application.

1 **Product Name and/or Model Numbers**

BECTON - DICKINSON SCF SYRINGES 1mL AND SYRINGE ROUND FLANGE LUER LOK.

Product No.

(max 250 characters)

Functional Description

GLASS SYRINGE BARRELS, WITH OR WITHOUT ATTACHED NEEDLE. NEEDLE SIZE OF 23G1, 25G5/8, 25G1. RUBBER NEEDLE SHIELDS GREY BUTYL STOPPERS AND POLYSTYRENE PLUNGER RODS THE ROUND FLANGE LUER SYRINGE HAS A POLYPROPYLENE BACKSTOP

ECRI - IMD Code

ECRI - IMD Code

Sterility Is this device, or any of its components, supplied sterile? Yes ☑ No ☐

Steam	☐ ST	Ethylene oxide	☑ EO	Filtration	☐ FT
Gamma irradiation	☑ GR	Dry heat	☐ DH	Other	☐

If OTHER, please specify (max 100 characters)

Source of Material Was material of human or other animal origin used in the manufacture and/or formulation of this device? Yes ☐ No ☑ Not applicable ☐ *(refer to Guide)*

specify types of animal origin

Office Use Only
Kit
N

Part 3 - Drug Product Details (*continued*)

1. Composite Packs Is this product a composite pack? Yes ☐ No ☑ *-If NO, go to "Dosage Form" details at item* **18**

- *If YES,* how many different drug components are there in this pack? ☐

Note: complete a copy of items 18 to 21 and 23 to 29 for each type of drug component and pin the extra pages to this one.

- Description of this drug component *(maximum 50 characters)*

Office use only

Dosage form NO CHANGES — Dosage Form code

18 Routes of administration

1. NO CHANGES — Admin. Route Code
2.
3.
4.

(max 150 characters)

26 Visual identification of dosage form NO CHANGES

21 Type of container in which this dosage form is to be supplied NO CHANGES — Container Code

(max 500 characters)

22 Proposed indications NO CHANGES

Part 3 - Drug Product Details *(continued)*

23 **Sterility** Is this product or any of its components, supplied sterile? **Yes** ☐ **No** ☐

Steam ☐ ST | Ethylene oxide ☐ EO | Filtration ☐ FT

Gamma irradiation ☐ GR | Dry heat ☐ DH | Other ☐ OT

If OTHER, please specify (max 100 characters)

24 **Proposed storage and shelf life**

- State the proposed temperature of storage of the product. *(Tick the appropriate box.)*

(i) Store below minus 18 degrees Celsius (deep freeze) ☐

(ii) Store below minus 5 degrees Celsius (freeze) ☐

(iii) Store below 8 degrees Celsius (refrigerate) ☐

(iv) Store at 2 to 8 degrees Celsius (refrigerate - do not freeze) ☐

(v) Store below 25 degrees Celsius ☐

(vi) Store below 30 degrees Celsius ☐

- State below whether any special additional storage precautions are necessary.

- State the proposed shelf life of the product. *(Tick the appropriate box)*

1 year ☐ 2 years ☐ 3 years ☐ 4 years ☐ 5 years ☐ Other *(please specify)* ☐

t

36 **Source of material** Was material of human or other animal origin used at any stage in the manufacture and/or formulation of these goods? **Yes** ☐ **No** ☐ **Not applicable** ☐

If YES, identify species

1. 2. 3.

Part 3 - Drug Product Details *(continued)*

26 **Printed product material supplied***

(Tick one or more boxes as relevant.)

container label		CL
primary pack label		PP
package insert		IN
promotional material		PM
product information	✓	PI
other *(please specify)*	✓	OT

t

Product Information in Module 1.3.1.1
Consumer Medicine Information in Module 1.3.2

* Attach to this page.

Part 4 - Formulation details

27 Active Ingredients

Note: *Attach additional pages as required.*

Names used must be those published in the Australian Approved Names Lists, unless no appropriate name exists in the lists.

Office Use Only

Name NO CHANGES

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Office Use Only

Number of active ingredients *(including equivalence statements)* listed for this drug component *(last page only)*.

Part 4 - Formulation details *(continued)*

28 Excipients

Attach additional pages as required.

Names used must be those published in the Australian Approved Names Lists, unless no appropriate name exists in the lists.

Note: *List proprietary ingredients, the formulations of which have not been or will not be revealed to you by your supplier(s) on page 10.*

Office Use Only

Name NO CHANGES

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Office Use Only

Number of non-proprietary excipient ingredients listed for this drug component *(last page only)*.

Part 4 - Formulation details *(continued)*

29 **Proprietary Ingredients - the formulations of which have not been or will not be revealed by you by your supplier(s)**

Note: *Attach additional pages as required.*

(max 65 characters)

Office Use Only

Proprietary Ingredient name NO CHANGES

Name of supplier

Supplier's Enterprise Identification Code *(if known)*

Proprietary Ingredient ARTG number *(if known)*

Proprietary Ingredient name

Name of supplier

Supplier's Enterprise Identification Code *(if known)*

Proprietary Ingredient ARTG number *(if known)*

Proprietary Ingredient name

Name of supplier

Supplier's Enterprise Identification Code *(if known)*

Proprietary Ingredient ARTG number *(if known)*

Proprietary Ingredient name

Name of supplier

Supplier's Enterprise Identification Code *(if known)*

Proprietary Ingredient ARTG number *(if known)*

Proprietary Ingredient name

Name of supplier

Supplier's Enterprise Identification Code *(if known)*

Proprietary Ingredient ARTG number *(if known)*

- Number of Proprietary ingredients listed for this drug component

- How many completed "Enterprise Details" forms have you attached for proprietary ingredient suppliers?

- Have you requested the suppliers of proprietary ingredients to advise the Australian Register of Therapeutic Goods of the composition of the proprietary ingredient on a "Notification of a Proprietary Ingredient" form?

Yes ☐ No ☐

Part 5 - Manufacturer details

Principal Manufacturer's Details

Note: Attach a copy of this section for each additional manufacturer.

34 **Principal manufacturer's business name** *(max 100 characters)* NO CHANGES

21 **Principal manufacturer's licence number** *(if applicable)*

32 **Principal manufacturer's enterprise identification code**

Office use only

Site Code

Alternative principal manufacturers

Note: Attach a copy of this section for each additional manufacturer.

33 **Alternative principal manufacturer's business name** *(max 100 characters)* NO CHANGES

34 **Alternative principal manufacturer's licence number** *(if applicable)*

Office use only

Site Code

35 **Alternative principal manufacturer's enterprise identification code**

Sub-manufacturers

Note: Attach a copy of this section for each additional sub-manufacturer.

33 **Sub-manufacturer's business name** *(max 100 characters)* NO CHANGES

37 **Sub-manufacture's licence number** *(if applicable)*

Office use only

Site Code

38 **Sub-manufacturer's enterprise identification code**

39 **Step in manufacture**

Part 8 - Overseas Manufacturer Details

40 Is evidence from a relevant overseas authority attached to establish that the principal manufacturer of the goods is of an acceptable standard?

N/A ☐ Yes ☐ No ☐ → *Attach separate sheet detailing reasons*

21 If documentation of the standard of the overseas manufacturer has previously been supplied as part of a successful application for registration or listing, state ARTG registration/listing number for the product here.

ARTG number

42 If acceptable documentation is not available, do you agree to pay the cost of an inspection of the principal overseas manufacturer by Australian inspectors if deemed necessary by the Secretary?

Yes ☐ No ☐ → *Attach separate sheet detailing reasons*

43 Has the overseas manufacturer agreed in writing to such an inspection?

Yes ☐ No ☐ → *Attach separate sheet detailing reasons*

Therapeutic Goods Act 1989

TGA Therapeutic Goods Administration

COMMONWEALTH DEPARTMENT OF HEALTH, HOUSING AND COMMUNITY SERVICES

Application – INFANRIX

(please tick the appropriate box)

☐ **for Registration (including Pharmaceutical Benefits Listing) of Drug Products**

☑ **to vary the Conditions of Registration of Drug Products**

(via Drug Evaluation Branch)

- To ensure this form is correctly completed, please refer to the explanatory guide issued for this application form before applying.
- Send **Original** of this form with a cheque for the appropriate fee(s) and an Enterprise Details form if necessary to:
  Note: Cheques should be made payable to: 'Therapeutic Goods Administration'.

via Courier

The Business Manager
Business Management Unit
Therapeutic Goods Administration
4th Floor, Alexander Building
Furzer Street
Phillip ACT
Australia

via Australia Post

The Business Manager
Business Management Unit
Therapeutic Goods Administration
PO Box 100
Woden ACT 2606
Australia

- Send a **copy** of this form with the Data for Evaluation to:

via Courier

The Director
Drug Evaluation Branch
5th Floor
Alexander Building
Furzer Street
Phillip ACT
Australia

via Australia Post

The Director
Drug Evaluation Branch
Therapeutic Goods Administration
PO Box 100
Woden ACT 2606
Australia

Part 1 - General Details

Sponsor details *(If an individual, provide full name; if a corporation, the registered company name under the Companies Code; or business names under which you propose to trade for the purposes of the Therapeutic Goods Act 1989.)*

Sponsor's business name *(max 100 characters)*

GLAXOSMITHKLINE AUSTRALIA PTY LTD

Sponsor's enterprise identification code

40010

Enterprise details

- Have you attached a completed "Enterprise Details" form? Yes ☐ No ☑

Payment enclosed *(for payment of relevant fees)*

$4,170.00

Sponsor Application and Declaration

- Sponsors should note that the *Therapeutic Goods Act 1989* provides penalties for making statements that are false or misleading in connection with an application for registration of therapeutic goods.

I apply to: *(delete whichever is not applicable)*

- ~~Register (including Pharmaceutical Benefits Listing)~~
- Vary the conditions of registration of

the goods described in this form and declare that the information given is, to the best of my knowledge, current and correct.

To the best of my knowledge, I certify that this application is accompanied by such information and in the required format as will allow the determination of the application (ie. complies with the current NDF guidelines for preparing applications to market drug products and any associated or supplementary guidelines). *(Refer to the Guide for details and Note on page 3 of this form.)*

Signature s22 [redacted]

Date 21 / 10 / 05 (dd / mm / yy)

Name *(please print)* s22 [redacted]

Position/ Relationship to Sponsor [redacted]

If you are not the Sponsor, have you attached a copy of a current "Instrument of Appointment" authorising you to act as a duly appointed agent of the Sponsor. Yes ☑ No ☐

Office Use Only

Receipt number		Charge code	
Fee	$	Correct fee	Yes ☐ No ☐
Enterprise ID			
TGAIN		ARTG no.	

Document 1

8 • Complete the authorisation below, or a copy, for each person you have appointed to submit applications for registration, listing or manufacturing licence on your behalf.

• Send the original authorisation to the *Therapeutic Goods Administration*. A copy of the authorisation should be included with each application (or group of applications) submitted by the authorised person on behalf of the enterprise.

Instrument of Appointment

• Please print full name where applicable.

I, s22 [redacted], GLAXOSMITHKLINE AUSTRALIA PTY LTD

being a sponsor or company director or company secretary of a sponsor of therapeutic goods in Australi

hereby appoint s22 [redacted]

as my/the sponsor's duly appointed agent to provide information and make declarations for the purpo of applications as required under the *Therapeutic Goods Act 1989*.

Signature s22 [redacted]

Date 9 / 7 / '02

• **Note:** If an individual person is the sponsor, this instrument is to be signed by that person; if a partnership, by a partner for the partnership; if a corporation, by a director of the company secretary of that corporation

Specimen signature of appointee s22 [redacted]

Signature of witness

Date 09 / 07 / 2002

Company Seal - if a corporation, place an imprint of the Company Seal here.

• When this instrument is revoked the enterprise must advise the *Therapeutic Goods Administration* in writing of th date of the revocation

Part 2 - Description of Data for Evaluation

6 Application types

- **Application to Register**

New Chemical or Biological Agent

1A new substance ☐

1B new salt or ester ☐

Other

2 new route of administration ☐

3 new combination ☐

5 Pharmaceutical Benefits Listing ☐

9 new strength ☐

10 new dosage form ☐

11 new generic product ☐

Indications

4A addition of new indication ☐

4B deletion of existing indication ☐

Other (continued)

12A formulation ☐

12I packaging ☐

12M other aspect of B1 data ☐

12N change to container ☐

- **Application to Vary Conditions**

Change in Pharmaceutical Data

12B specifications - raw material drug ☐

12C specifications - finished product ☐

12D specification - excipients ☐

12E synthetic route - raw material drug ☐

12F manufacturing procedure - finished product ☐

12G site of manufacture - raw material drug ☐

12H site of manufacture - finished product ☐

12I packaging ☐

12J additional pack size(s) in existing materials ☐

12K shelf life and/or storage conditions ☐

12L labelling ☐

12M other aspects of B1 data ☐

Other

2 new route of administration ☐

6 change in regulatory status ☐

7 change in dosage, dose regimen or maximum daily dose ☐

7A change in patient group ☐

13 not in 1 to 12 ☐

Change in Product Information

8A clinical aspects - safety related ☐

8B clinical aspects - non-safety related ☑

8C preclinical aspects (B2) ☐

8D pharmaceutical aspects (B1) ☐

8E other P1 ☐

Part 2 - Description of Data for Evaluation (*continued*)

If you consider you have not supplied such information as will allow the determination of the application, please attach a separate sheet detailing reasons.

7 Details of Data submitted

Section	Number of volumes	Number of pages	Number of copies
Pharmaceutical (B1)	-	-	-
Preclinical (B2)	-	-	-
Clinical (B3) Module 5	2	-	1
Summary (C) Module 1	1	-	4
Module 2	1	-	4
Bioavailability			
Product information	In Module 1		
Other (specify)			

- Is this application in support of an application for pharmaceutical benefits listing? Yes [ ] No [✓]

9 Relevant TGA file numbers/control numbers from previous correspondence

9 Is the product in this application to replace an existing ARTG entry?

Yes [ ] No [✓]

↓

Current ARTG Registration No. of the existing entry *(see Guide)* [ ]

10 Export names

Do you intend to export this product using a different name from the registration name?

Yes [ ] No [✓] *If NO*, go to item **11**

↓

State the export name(s) to be used for this product

Export name	**1.**
	2.
	3.
	4.
	5.

11 **Exchange of Evaluation Reports**

Do you give approval for exchange of evaluation reports with other regulatory agencies for this submission? **Yes** ✓ **No**

Signature s22 [redacted]

Date 21 / 10 / 05
dd mm yy

Name *(please print)* s22 [redacted]

Position/Relationship to Sponsor [redacted]

Office Use Only

DEB

Control number

Application number

Part 3 - Drug Product Details

12 **Registration name (product name in Australia)** *(max 100 characters)*

INFANRIX 0.5mL injection vial

INFANRIX 0.5mL injection syringe

13 **Code name**

14 **Relevant ARTG Registration number(s)**

1. 54084	2. 54085	3.	4.

15 **Category of Therapeutic Goods** Goods included in this application:

Drugs only ☐ - Go to item **16**

Drug-Device combinations ***(Drugs supplied in a therapeutic device)*** ☑

- attach a supplement for Therapeutic Devices form

Drugs supplied as a component of a therapeutic device kit ☐

- attach a supplement for Therapeutic Devices form

Office Use Only

	Drug	Device
Defn	Y	N
Data	Y	
ADG		

Is a supplement for "Therapeutic Devices form" attached to this page? **Yes** ☑ **No** ☐

16 **Pack Size and Poisons schedule**

Pack/container sizes in which this product is supplied	**SUSDP Schedule No. for this pack size** ***(If not scheduled write "N")***
1. NO CHANGES	
2.	
3.	
4.	
5.	

Pin extra pages here

Document 1

Therapeutic Device Supplement

Office Use Only

ARTG No.

ADG

1 **Category of Therapeutic Drug-Device Combination**

Products included in this application:

☑ Devices supplied in a drug – device combination - *complete Supplement part 1*

☐ Devices supplied as components of a therapeutic device kit, tray or pack - *complete Supplement part 2*

2 **Registration/ Listing name**

INFANRIX 0·5mL injection syringe

NO CHANGE

Device in a Drug - Device Combinations

Part 1

Office Use Only

Individual device details

Attach a copy of Part 1 for each individual therapeutic device product included as part of the drug-device combination in the drug application.

Product Name and/or Model Numbers

BECTON-DICKINSON SCF SYRINGES 1mL AND SYRINGE ROUND FLANGE LUER LOK.

(max 250 characters)

Product No.

Functional Description

GLASS SYRINGE BARRELS, WITH OR WITHOUT ATTACHED NEEDLE. NEEDLE SIZE OF 23G1, 25GS/S, 25G1. RUBBER NEEDLE SHIELDS GREY BUTYL STOPPERS AND POLYSTYRENE PLUNGER RODS. THE ROUND FLANGE LUER SYRINGE HAS A POLYPROPYLENE BACKSTOP

ECRI - IMD Code

ECRI - IMD Code

Sterility Is this device, or any of its components, supplied sterile?

Yes ☑ No ☐

Steam	☐ ST	Ethylene oxide	☑ EO	Filtration	☐ FT
Gamma irradiation	☑ GR	Dryheat	☐ DH	Other	☐☐

If OTHER, please specify (max 100 characters)

Source of Material Was material of human or other animal origin used in the manufacture and/or formulation of this device?

Yes ☐ No ☑ Not applicable ☐ *(refer to Guide)*

If specify types of animal origin

Office Use Only

Kit

N

Part 3 - Drug Product Details (*continued*)

Composite Packs Is this product a composite pack? Yes ☐ No ☑ *-If NO, go to "Dosage Form" details at item* **18**

- *If YES,* how many different drug components are there in this pack? ☐

  Note: complete a copy of items 18 to 21 and 23 to 29 for each type of drug component and pin the extra pages to this one.

- Description of this drug component *(maximum 50 characters)*

Office use only

18 **Dosage form** NO CHANGES — Dosage Form code

19 **Routes of administration**
1. NO CHANGES — Admin. Route Code
2.
3.
4.

(max 150 characters)

20 **Visual identification of dosage form** NO CHANGES

21 **Type of container in which this dosage form is to be supplied** NO CHANGES — Container Code

(max 500 characters)

22 **Proposed indications** NO CHANGES

Part 3 - Drug Product Details *(continued)*

23 **Sterility** Is this product or any of its components, supplied sterile? Yes ☐ No ☐

Steam ☐ ST | Ethylene oxide ☐ EO | Filtration ☐ FT

Gamma irradiation ☐ GR | Dry heat ☐ DH | Other ☐ OT

If OTHER, please specify (max 100 characters)

24 **Proposed storage and shelf life**

- State the proposed temperature of storage of the product. *(Tick the appropriate box.)*

(i) Store below minus 18 degrees Celsius (deep freeze) ☐

(ii) Store below minus 5 degrees Celsius (freeze) ☐

(iii) Store below 8 degrees Celsius (refrigerate) ☐

(iv) Store at 2 to 8 degrees Celsius (refrigerate - do not freeze) ☐

(v) Store below 25 degrees Celsius ☐

(vi) Store below 30 degrees Celsius ☐

- State below whether any special additional storage precautions are necessary.

- State the proposed shelf life of the product. *(Tick the appropriate box)*

1 year ☐ 2 years ☐ 3 years ☐ 4 years ☐ 5 years ☐ Other *(please specify)* ☐

t

21 **Source of material** Was material of human or other animal origin used at any stage in the manufacture and/or formulation of these goods? Yes ☐ No ☐ Not applicable ☐

If YES, identify species

1. 2. 3.

Part 3 - Drug Product Details *(continued)*

26 **Printed product material supplied***

(Tick one or more boxes as relevant.)

container label		CL
primary pack label		PP
package insert		IN
promotional material		PM
product information	✓	PI
other *(please specify)*	✓	OT

Product Information in Module 1.3.1.1
Consumer Medicine Information in Module 1.3.2

* Attach to this page.

Part 4 - Formulation details

27 Active Ingredients

Note: *Attach additional pages as required.*

Names used must be those published in the Australian Approved Names Lists, unless no appropriate name exists in the lists.

			Office Use Only
Name	NO CHANGES		
Quantity		Units	
Name			
Quantity		Units	
Name			
Quantity		Units	
Name			
Quantity		Units	
Name			
Quantity		Units	
Name			
Quantity		Units	
Name			
Quantity		Units	
Name			
Quantity		Units	
Name			
Quantity		Units	

Office Use Only

Number of active ingredients *(including equivalence statements)* listed for this drug component *(last page only)*.

Part 4 - Formulation details *(continued)*

28 Excipients

Attach additional pages as required.

Names used must be those published in the Australian Approved Names Lists, unless no appropriate name exists in the lists.

Note: *List proprietary ingredients, the formulations of which have not been or will not be revealed to you by your supplier(s) on page 10.*

Office Use Only

Name NO CHANGES

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Name

Quantity Units

Office Use Only

Number of non-proprietary excipient ingredients listed for this drug component *(last page only)*.

Part 4 - Formulation details *(continued)*

29 **Proprietary Ingredients - the formulations of which have not been or will not be revealed by you by your supplier(s)**

Note: *Attach additional pages as required.*

(max 65 characters)

Office Use Only

Proprietary Ingredient name NO CHANGES

Name of supplier

Supplier's Enterprise Identification Code *(if known)*

Proprietary Ingredient ARTG number *(if known)*

Proprietary Ingredient name

Name of supplier

pplier's Enterprise Identification Code *(if known)*

Proprietary Ingredient ARTG number *(if known)*

Proprietary Ingredient name

Name of supplier

Supplier's Enterprise Identification Code *(if known)*

Proprietary Ingredient ARTG number *(if known)*

Proprietary Ingredient name

Name of supplier

Supplier's Enterprise Identification Code *(if known)*

Proprietary Ingredient ARTG number *(if known)*

Proprietary Ingredient name

Name of supplier

Supplier's Enterprise Identification Code *(if known)*

Proprietary Ingredient ARTG number *(if known)*

- Number of Proprietary ingredients listed for this drug component

- How many completed "Enterprise Details" forms have you attached for proprietary ingredient suppliers?

- Have you requested the suppliers of proprietary ingredients to advise the Australian Register of Therapeutic Goods of the composition of the proprietary ingredient on a "Notification of a Proprietary Ingredient" form?

Yes ☐ No ☐

Part 5 - Manufacturer details

ipal Manufacturer's Details

Attach a copy of this section for each additional manufacturer.

		(max 100 characters)
30	Principal manufacturer's business name	NO CHANGES
31	Principal manufacturer's licence number *(if applicable)*	
32	Principal manufacturer's enterprise identification code	

Office use only

Site Code

native principal manufacturers

Note: Attach a copy of this section for each additional manufacturer.

		(max 100 characters)
33	Alternative principal manufacturer's business name	NO CHANGES
34	Alternative principal manufacturer's licence number *(if applicable)*	
35	Alternative principal manufacturer's enterprise identification code	

Office use only

Site Code

-manufacturers

Note: Attach a copy of this section for each additional sub-manufacturer.

		(max 100 characters)
36	Sub-manufacturer's business name	NO CHANGES
37	Sub-manufacture's licence number *(if applicable)*	
38	Sub-manufacturer's enterprise identification code	
39	Step in manufacture	

Office use only

Site Code

Part 6 - Overseas Manufacturer Details

40 Is evidence from a relevant overseas authority attached to establish that the principal manufacturer of the goods is of an acceptable standard?

N/A ☐ Yes ☐ No ☐ → *Attach separate sheet detailing reasons*

21 If documentation of the standard of the overseas manufacturer has previously been supplied as part of a successful application for registration or listing, state ARTG registration/listing number for the product here.

ARTG number

42 If acceptable documentation is not available, do you agree to pay the cost of an inspection of the principal overseas manufacturer by Australian inspectors if deemed necessary by the Secretary?

Yes ☐ No ☐ → *Attach separate sheet detailing reasons*

43 Has the overseas manufacturer agreed in writing to such an inspection?

Yes ☐ No ☐ → *Attach separate sheet detailing reasons*

INFANRIX HEXA Product Information

INFANRIX® hexa

Combined Diphtheria-Tetanus-acellular Pertussis (DTPa), Hepatitis B, Poliovirus and *Haemophilus influenzae* type b vaccine

DESCRIPTION

INFANRIX hexa vaccine is a sterile suspension which contains diphtheria toxoid, tetanus toxoid, three purified antigens of *Bordetella pertussis* [pertussis toxoid (PT), Pertussis filamentous haemagglutinin (FHA) and pertactin (PRN)], the purified major surface antigen (HBsAg) of the hepatitis B virus (HBV) and purified polyribosyl-ribitol-phosphate (PRP) capsular polysaccharide of *Haemophilus influenzae* type b (Hib), covalently bound to tetanus toxoid, adsorbed on aluminium salts. It also contains three types of inactivated polio viruses (type 1: Mahoney strain; type 2: MEF-1 strain; type 3: Saukett strain).

The diphtheria and tetanus toxoids are obtained by formaldehyde treatment of purified *Corynebacterium diphtheriae* and *Clostridium tetani* toxins. The acellular pertussis vaccine components are obtained by extraction and purification from phase I *Bordetella pertussis* cultures, followed by irreversible detoxification of the pertussis toxin by glutaraldehyde and formaldehyde treatment, and formaldehyde treatment of FHA and PRN.

The surface antigen of the HBV (HBsAg) is produced by culture of genetically-engineered *Saccharomyces cerevisiae* yeast cells which carry the gene coding for the major surface antigen of the HBV. This HBsAg expressed in yeast cells is purified by several physico-chemical steps.

The three polioviruses are cultivated on a continuous VERO cell line, purified and inactivated with formaldehyde.

The Hib polysaccharide is prepared from Hib, strain 20,752 and after activation with cyanogen bromide and derivatisation with an adipic hydrazide spacer is coupled to tetanus toxoid via carbodiimide condensation. After purification the conjugate is adsorbed on aluminium salt, and then lyophilised in the presence of lactose as stabiliser.

A 0.5 mL dose of vaccine contains not less than 30IU (25Lf U) of diphtheria toxoid, not less than 40IU (10Lf U) of tetanus toxoid 25µg of PT, 25µg of FHA, 8µg of PRN, 10µg of recombinant HBsAg protein, 40 D-antigen units of type 1 (Mahoney), 8 D-antigen units of type 2 (MEF-1) and 32 D-antigen units of type 3 (Saukett) of the polio virus. It also contains 10µg of purified capsular polysaccharide of Hib (PRP) covalently bound to 20-40µg tetanus toxoid (T). The final vaccine is formulated in saline and contains 2-phenoxyethanol.

The manufacture of this product includes exposure to bovine derived materials. No evidence exists that any case of vCJD (considered to be the human form of bovine spongiform encephalopathy) has resulted from the administration of any vaccine product.

INFANRIX hexa meets the World Health Organisation requirements for manufacture of biological substances, of diphtheria, tetanus, pertussis and combined vaccines, of hepatitis B vaccines made by recombinant DNA techniques, of inactivated poliomyelitis vaccines and of Hib conjugate vaccines.

CLINICAL PHARMACOLOGY

Clinical Trials

Primary Immunisation - Immunogenicity Studies

The immunogenicity of *INFANRIX hexa* has been evaluated in >2390 infants during clinical trials. In these studies, *INFANRIX hexa* was shown to induce antibodies against all of the components contained in the vaccine. A variety of primary vaccination schedules were used including vaccination at 2, 4 and 6 months and at 3, 4 and 5 months. Immune responses from a pivotal clinical study using a 2, 4, 6 month schedule are presented in the following table.

Immune responses # one month following primary vaccination with INFANRIX hexa vaccine at 2, 4, 6 months of age

Antigen (n)	Antibody response (% Seropositive)	GMT [95% confidence intervals]
Diphtheria toxoid (n= 985)	99.6 [99.0 – 99.9]	1.31 IU/mL [1.24 – 1.39]
Tetanus toxoid (n= 985)	100 [99.6 – 100.0]	2.27 IU/mL [2.17 – 2.38]
Hepatitis B (n= 989)	98.5 [97.5 – 99.1]	1157.2 mIU/mL [1049.6 – 1275.7]
Pertussis toxoid (n= 986)	100.0 [99.6 – 100.0]	74.3 EL.U/mL [71.4 – 77.3]
Pertussis FHA (n= 917)	100.0 [99.6 – 100.0]	315.0 EL.U/mL [303.1 – 327.5]
Pertactin (n=990)	99.8 [99.3 – 100.0]	116.9 EL.U/mL [110.7 – 123.4]
Poliovirus type 1 (n=953)	99.7 [99.1 – 99.9]	458.1 [422.2 497.0]
Poliovirus type 2 (n=952)	99.9 [99.4 – 100.0]	425.1 [393.0 – 459.8]
Poliovirus type 3 (n=939)	99.9 [99.4 – 100.0]	933.0 [863.4 – 1008.2]
Hib PRP capsular polysaccharide (n=865)	95.9 [94.5– 97.1]	2.53 [2.31 – 2.77]

n = number of subjects tested
# = ITT cohort for immunogenicity
IU = International Units; EL.U = ELISA Units.
The cut-off values for diphtheria and tetanus (≥0.1 IU/mL), hepatitis B (≥10 mIU/mL), PRP-T (≥0.15µg/mL) and the three poliovirus serotypes (≥8) correlate with seroprotection.
The results for poliovirus are expressed as a titre which is the reciprocal of the highest dilution of serum showing 50% virus neutralisation effect in a microneutralisation test.
Currently there are no known serological correlates for protection for the pertussis antigens. The assay cutoff used for the pertussis antigens is ≥5 EL.U/mL.

Protective efficacy against pertussis following primary immunisation - INFANRIX® (DTPa)

The protective efficacy of *INFANRIX®* (DTPa) following primary immunisation has been established using WHO-defined typical pertussis (≥21 days of paroxysmal cough with laboratory confirmation) in two clinical studies.

In a prospective blinded household contact study conducted in Germany, data were collected from 360 evaluable secondary contacts in households where there was an index case of typical pertussis. Vaccine efficacy was calculated at 88.7% with a two sided 95% confidence interval of 76.6% to 94.5%. This was not statistically different from the DTPw vaccine used in the trial.

In a randomised, double-blind, controlled clinical study conducted in Italy, infants were administered three doses of *INFANRIX®* at 2, 4 and 6 months of age, and followed for an average of 17 months (n=5951). *INFANRIX®* vaccine efficacy was calculated to be 83.9% with a two sided 95% confidence interval of 75.8% to 89.4% against pertussis.

In a follow-up of the same cohort, the efficacy for *INFANRIX®* vaccine was found to be 86% up to 6 years of age.

Protective efficacy against *Haemophilus influenzae* type b following primary immunisation – field effectiveness

The humoral immune response (as measured by serum antibody levels) is complemented by the induction of a cellular immune response (including immune memory), which has been shown to be present as early as four months after completion of the primary immunisation schedule with *INFANRIX hexa*. Data from field studies in the UK have shown that Hib vaccine effectiveness remains high for several years after primary vaccination, despite low levels of serum antibodies, and without administration of a booster dose. Immune memory has thus been proposed as an important mechanism resulting in the long term protection against invasive Hib disease seen in these studies.

The effectiveness of GSK's Hib component (when combined with DTPa based vaccines) has been, and continues to be investigated via an extensive post-marketing surveillance study conducted in Germany. Over a 2 year follow-up period, the effectiveness of three primary doses of GSK's DTPa/Hib and DTPa-IPV/Hib was found to be 98.8%

As the antigen components of the vaccines are identical, it is expected that efficacy data from GSK's DTPa and DTPa/Hib conjugate combination studies can be extrapolated to *INFANRIX hexa*, and that *INFANRIX hexa* will provide similar protective efficacy against pertussis and Hib disease.

Booster dosing - following primary *INFANRIX hexa* vaccination

The response to a booster dose of *INFANRIX hexa* during the second year of life has been evaluated in 307 children. The following table presents data from a booster with *INFANRIX hexa*. These infants were primed with *INFANRIX hexa* at 3, 4 and 5 months.

Immune responses# one month following administration of INFANRIX hexa vaccine as a booster dose in children in their second year of life following primary vaccination with INFANRIX hexa at 3, 4 and 5 months

Antigen (n)	Antibody response (% seropositive)		GMT [95% confidence interval]	
	Pre-booster	Post-booster	Pre-booster	Post-booster
Diphtheria toxoid (330)	58.9 [53.4 – 64.2]	100.0 [98.9 – 100.0]	0.12 [0.11 – 0.14]	3.63 [3.28 – 4.01]
Tetanus toxoid (330)	89.5 [85.7 – 92.6]	100.0 [98.9 – 100.0]	0.28 [0.25 – 0.31]	4.70 [4.32 – 5.11]
Hepatitis B (326)	96.7 [94.2 – 98.3]	98.8 [96.9 – 99.7]	149.5 [129.5 – 172.8]	3711.2 [3066.3 – 4491.7]
Pertussis toxoid (330)	75.6 [70.6 – 80.1]	100.0 [98.9 – 100.0]	8.2 [7.5 – 9.1]	86.9 [80.1 – 94.3]
Pertussis FHA (328)	99.7 [98.3 – 100.0]	100.0 [98.9 – 100.0]	38.5 [35.2 – 42.1]	425.5 [395.3 – 458.1]
Pertactin (330)	88.6 [84.7 – 91.8]	100.0 [98.9 – 100.0]	17.5 [15.6 – 19.7]	398.5 [362.3 – 438.4]
Poliovirus type 1 (302)	93.4 [90.1 – 95.9]	100.0 [98.8 – 100.0]	66.7 [56.8 – 78.2]	1291.4 [1148.8 – 1451.6]
Poliovirus type 2 (292)	92.3 [88.7 – 95.1]	100.0 [98.7 – 100.0]	47.6 [40.8 – 55.6]	1601.7 [1419.0 – 1807.8]
Poliovirus type 3 (300)	98.7 [96.7 – 99.6]	100.0 [98.8 – 100.0]	128.9 [111.9 – 148.4]	3103.0 [2800.8 – 3437.9]
Hib PRP capsular polysaccharide (330)	84.0 [79.6 – 87.8]	99.4 [97.8 - 99.9]	0.54 [0.47 – 0.62]	45.40 [38.94 – 52.94]

n = number of subjects tested post-booster.
# = ITT cohort for immunogenicity
IU = International Units; EL.U = ELISA Units;
The cut-off values for diphtheria and tetanus (≥0.1 IU/mL), hepatitis B (≥10 mIU/mL), the three poliovirus serotypes (≥8) and PRP (≥0.15ug/mL) correlate with seroprotection.
The results for poliovirus are expressed as a titre which is the reciprocal of the highest dilution of serum showing 50% virus neutralisation effect in a microneutralisation test.
Currently there are no known serological correlates for protection for the pertussis antigens. The assay cutoff used for the pertussis antigens is (≥5 EL.U/mL).

INDICATIONS

INFANRIX hexa is indicated for primary immunisation of infants from the age of 6 weeks against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, and *Haemophilus influenzae* type b.

INFANRIX hexa is also indicated for use as a booster dose at 18 months of age if boosting with hepatitis B, poliomyelitis, and *Haemophilus influenzae* type b, as well as diphtheria, tetanus and pertussis is required.

CONTRAINDICATIONS

INFANRIX hexa should not be administered to subjects with known hypersensitivity to any components of the vaccine, or to subjects having shown signs of hypersensitivity after previous administration of diphtheria, tetanus, pertussis, hepatitis B, polio or Hib vaccines.

INFANRIX hexa is contraindicated if the child has experienced encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis containing vaccine. In these circumstances pertussis vaccination should be discontinued and the vaccination should be continued with diphtheria-tetanus, hepatitis B, inactivated polio and Hib vaccines.

PRECAUTIONS

***INFANRIX hexa* should under no circumstances be administered intravenously.**

It is good clinical practice that immunisation should be preceded by a review of the medical history (especially with regard to previous immunisation and possible occurrence of undesirable events) and a clinical examination.

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic reaction following the administration of the vaccine.

If any of the following events are known to have occurred in temporal relation to receipt of whole cell or acellular pertussis-containing vaccine, the decision to give further doses of vaccine containing the pertussis component should be carefully considered. No data currently exist on use of *INFANRIX hexa* in these children. There may be circumstances,

such as a high incidence of pertussis, when the potential benefits outweigh possible risks, particularly since these events are not associated with permanent sequelae.

- Temperature of ≥40.5°C within 48 hours, not due to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours.
- Persistent, inconsolable crying lasting ≥ 3 hours, occurring within 48 hours.
- Convulsions with or without fever, occurring within 3 days.

A history of febrile convulsions, a family history of convulsions, a family history of Sudden Infant Death Syndrome (SIDS) and a family history of an adverse event following INFANRIX hexa vaccination do not constitute contra-indications.

As with other vaccines, the administration of *INFANRIX hexa* should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection, however, is not a contraindication.

INFANRIX hexa should be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular injection in these subjects.

INFANRIX hexa should not be administered at birth. Infants born of HBsAg positive mothers should receive hepatitis B immune globulin and hepatitis B vaccine at birth.

The immune response to some Hib conjugate vaccines has been reported to be reduced in infants born prematurely compared to term infants. There are no data on the use of *INFANRIX hexa* in infants born prematurely.

INFANRIX hexa contains traces of neomycin and polymyxin. The vaccine should be used with caution in patients with known hypersensitivity to one of these antibiotics.

Human Immunodeficiency Virus (HIV) infection is not considered as a contra-indication. However in patients with immunodeficiency or in patients receiving immunosuppressive therapy, the expected immunologic response may not be achieved. No data currently exist on use of *INFANRIX hexa* in these patients.

The vaccine will not prevent infection caused by other agents such as hepatitis A, hepatitis C and hepatitis E and other pathogens known to infect the liver.

As hepatitis D (caused by the delta agent) does not occur in the absence of hepatitis B infection, it can be expected that hepatitis D will also be prevented by vaccination with *INFANRIX hexa*.

The Hib component of the vaccine does not protect against diseases due to other strains of *Haemophilus influenzae* or against meningitis caused by other organisms.

Excretion of capsular polysaccharide antigen in the urine has been described following receipt of Hib vaccines, and therefore antigen detection may be less specific in suspected Hib disease occurring within 1-2 weeks of vaccination.

Native populations (native Alaskans, native American Indians) with a high incidence of *Haemophilus influenzae* type b disease have shown a reduced antibody response to *Haemophilus influenzae* type b conjugate vaccines. The immunogenicity of *INFANRIX hexa* has not been studied in the Australian indigenous population. There are no data to support the immunogenicity of *INFANRIX hexa* for anti-PRP antibodies after 1 dose at 2 months or two doses at 4 months of age. Prior to introduction of Hib vaccination the incidence of Hib disease in indigenous Australian children was considerably higher than in non-indigenous Australian children, and onset of Hib disease in indigenous children was at a much earlier age (e.g. 60% under 6 months of age in remote rural areas). *INFANRIX hexa* is not recommended for use in indigenous Australian populations.

Use In Pregnancy (Category B2)

As *INFANRIX hexa* is not intended for use in adults, adequate human data on use during pregnancy and adequate animal reproduction studies are not available.

Use In Lactation

As *INFANRIX hexa* is not intended for use in adults, adequate human data on use during lactation are not available.

Interactions

INFANRIX hexa should not be mixed with other vaccines in the same syringe.

ADVERSE REACTIONS

INFANRIX hexa has been assessed for safety and reactogenicity in controlled clinical trials in over 6000 infants. Diary cards were used to actively monitor signs and symptoms following vaccination.

Primary Immunisation

In a large clinical study involving 1076 subjects, the following solicited symptoms were reported within 48 hours following vaccination with *INFANRIX hexa* or following separate administration of DTPa, hepatitis B, Hib and oral polio vaccines. The incidence of solicited symptoms following vaccination with *INFANRIX hexa* was compared to concomitant administration of *INFANRIX*, Hepatitis B, oral polio vaccine and Hib vaccine. No significant difference in the frequency of solicited symptoms was observed between the *INFANRIX hexa* group and the comparator groups. Virtually all symptoms reported resolved within four days and all subjects recovered without sequelae. A causal relationship between vaccine use and the recorded event has not been established for each individual event.

Incidence (%) of solicited symptoms reported within 48 hours following primary immunisation with INFANRIX hexa in a comparative clinical study using a 2, 4, 6 month schedule

Solicited symptoms	**INFANRIX hexa**	**DTPa(INFANRIX™) + HepB(ENGERIX-B™) + Hib(OmniHIB®) + OPV(ORIMUNE®)**			
Local reactions:	**N=3058**	**N=975**			
		Any site	**INFANRIX™**	**ENGERIX-B™**	**OmniHIB®**
Pain at the injection site:	20.6	27.6	20.2	23.5	19.0
Redness ≥20mm	1.7	2.1	1.2	1.3	0.7
Swelling ≥20mm	2.9	2.2	1.2	1.4	0.6
General symptoms:	**N=3063**	**N=978**			
Fever:					
Any#	18.1	17.1			
Grade 3@	0.5	0.3			
Drowsiness	38.9	43.1			
Irritability	55.0	57.5			
Loss of appetite	17.4	18.5			

N = Total number of doses administered
 # = A temperature of ≥37.5°C (axillary or oral) or ≥38°C (rectal)
@ = A temperature of ≥39.1°C (axillary or oral) or ≥39.6°C (rectal)

Booster Immunisation

The table below summarises the incidence of solicited symptoms reported during the first four days following a booster dose of *INFANRIX hexa* in children aged 12-18 months. The majority of symptoms were mild, and all subjects recovered without sequelae. A causal relationship between vaccine use and the recorded event has not been established for each individual event.

Incidence (%) of solicited symptoms following a booster immunisation with INFANRIX hexa in children aged 12-18 months

Solicited symptoms	**% Incidence**
Local reactions:	**(N=337)**
Pain at the injection site:	38.9
Redness >20mm	11.0
Swelling >20mm	10.4
General symptoms:	**(N=338)**
Fever: Any# Grade 3@	 45.9 4.4
Drowsiness	38.5
Irritability	45.6
Loss of appetite	28.7

N = Number of subjects with at least one symptom sheet completed
 # = A temperature of ≥37.5°C (axillary or oral) or ≥38°C (rectal)
@ = A temperature of ≥39.0°C (axillary or oral) or ≥39.5°C (rectal)

Other events

The following unsolicited events have been reported in clinical trials or reported during post marketing surveillance. It should be noted that causality has not necessarily been established for these events.

Events are listed within body systems and categorised by frequency according to the following definitions: ***very common* events reported at a frequency of greater or equal to 1/10 patients;** *common* events reported at a frequency of **less than 1/10 but** greater or equal to 1/100 patients; *uncommon* events reported at a frequency of less than 1/100 but greater or equal to 1/1,000 patients; *rare* events reported at a frequency of less than

1/1,000 patients **but greater or equal to 1/10,000 patients; *very rare* events reported at a frequency of less than 1/10,000 patients**.

Injection site: ***Very common:* local swelling at the injection site ≤ 50mm***
Common: injection site mass, **local swelling at the injection site >50mm***
Uncommon:* diffuse swelling of the injected limb, sometimes involving the adjacent joint
***Very rare:* swelling of the entire injected limb has been observed during post-marketing surveillance**

Body as a whole: *Common*: unusual crying, restlessness
Uncommon: fatigue
Very rare: allergic reactions (including rash and pruritis) and anaphylactoid reactions (including urticaria)

Central Nervous System: *Common*: nervousness
Uncommon: somnolescence
Very rare: convulsions (with or without fever)

Gastrointestinal system: *Common:* diarrhoea, enteritis, gastroenteritis,
Uncommon: abdominal pain, vomiting, constipation

Resistance mechanism: *Common*: upper respiratory tract infection

Respiratory system: *Common*: bronchitis, rhinitis
Uncommon: bronchospasm, laryngitis, stridor

Vision: *Uncommon:* conjunctivitis

During clinical trials, it has been observed that children primed with acellular pertussis vaccines are more likely to experience swelling reactions after booster administration in comparison with children primed with whole cell vaccines. These reactions resolve over an average of 4 days.

As for other DTPa vaccines, a slight increase in reactogenicity was reported after booster vaccination, with a low incidence of symptoms graded as severe.

~~Large oedematous swelling leading to an increased circumference of the injected limb has been observed in clinical trial studies of booster doses of *INFANRIX*®, with an incidence of approximately 1%, and has also been reported to date following booster administration of INFANRIX hexa. All these larger reactions with *INFANRIX*® resolved without sequelae.~~

Very rare cases of collapse or shock-like state (hypotonic-hyporesponsiveness episode) within 2 to 3 days of vaccination have been reported in subjects who

have received *INFANRIX®* combination vaccines. All the subjects recovered without sequelae.

DOSAGE AND ADMINISTRATION

Before use of the vaccine, the *INFANRIX hexa* suspension should be well shaken in order to obtain a homogeneous turbid white suspension. The *INFANRIX hexa* suspension and the Hib pellet should be inspected visually for any foreign particulate matter or discolouration prior to administration. In the event of either being observed, discard the vaccine.

The vaccine must be reconstituted by adding the entire contents of the supplied syringe containing the liquid component to the vial (or vial with Bioset™) containing the Hib pellet.

Vial. After the addition of the liquid component to the pellet, the mixture should be well shaken until the pellet is completely dissolved.

Vial with Bioset™. The Hib pellet is accessed by twisting and removing the plastic cover from the vial with the Bioset™ cap. The syringe containing the liquid suspension must be fixed with slight pressure onto the Bioset™ containing the Hib pellet. A "click" sound indicates activation of the system. The liquid suspension (which is cloudy) is injected into the vial containing the Hib pellet. Holding the syringe in place, the vial must be agitated until the Hib pellet is completely dissolved. The reconstituted vaccine should be drawn back into the syringe. The syringe must be removed from the Bioset™ by simply pulling to separate and a needle affixed for vaccine administration.







The reconstituted vaccine presents as a slightly more cloudy suspension than the liquid component alone. This is normal and does not impair the performance of the vaccine. In the event of other variation being observed, discard the vaccine.

After reconstitution, the vaccine should be injected promptly. However, the vaccine may be kept for up to 8 hours at room temperature.

Dosage

Each dose consists of a 0.5mL ready to use sterile suspension.

Administration

INFANRIX hexa is administered by intramuscular injection. THE VACCINE SHOULD NEVER BE ADMINISTERED INTRAVENOUSLY.

INFANRIX hexa should be injected intramuscularly in the anterolateral aspect of the thigh or the deltoid region of the arm. The recommended dose (0.5mL) of vaccine must be administered.

Immunisation Schedule

The primary immunisation course of *INFANRIX hexa* consists of three doses. *INFANRIX hexa* is recommended for administration at 2, 4 and 6 months of age.

INFANRIX hexa can be given as a booster dose at 18 months of age when boosting with hepatitis B, and/or poliomyelitis and/or *Haemophilus influenzae* type b, as well as diphtheria, tetanus and pertussis is required. For example, this may be appropriate for some children who need a hepatitis B booster dose following an accelerated hepatitis B immunisation schedule (such as 3 doses at 1 month intervals). There is no theoretical concern regarding receipt of an additional dose of hepatitis B, inactivated poliovirus, or Haemophilus influenzae type b vaccines.

STORAGE

The vaccine should be stored between +2°C and +8°C. DO NOT FREEZE. The *INFANRIX hexa* suspension and the reconstituted vaccine must not be frozen. Discard if vaccine has been frozen. Protect from light.

The expiry date of the vaccine is indicated on the label and packaging.

PRESENTATIONS

INFANRIX hexa is presented as a turbid white suspension in a pre-filled syringe. Upon storage, a white deposit and clear supernatant can be observed.

The lyophilised Hib vaccine is presented as a white pellet in a glass vial, or in a glass vial with Bioset™.

The vials and syringes are made of neutral glass type I, which conforms to European Pharmacopoeia Requirements.

This combination pack is supplied in packs of 1's or packs of 10's.

MANUFACTURER:

GlaxoSmithKline Biologicals
Rue de l'Institut 89
1330 Rixensart, Belgium.

DISTRIBUTED IN AUSTRALIA BY:

GlaxoSmithKline Australia Pty. Ltd.
1061 Mountain Highway
Boronia VIC 3155

TGA Approval date: TBA

Issue 4

® INFANRIX is a registered trademark of the GlaxoSmithKline group of companies

INFANRIX PENTA Product Information

INFANRIX® PENTA

Combined Diphtheria-Tetanus-acellular Pertussis (DTPa), Hepatitis B and Inactivated Poliovirus Vaccine

DESCRIPTION

INFANRIX® PENTA vaccine is a sterile suspension which contains diphtheria toxoid, tetanus toxoid, three purified antigens of *Bordetella pertussis* [pertussis toxoid (PT), pertussis filamentous haemagglutinin (FHA) and pertactin (PRN)] and the purified major surface antigen (HBsAg) of the hepatitis B virus (HBV), adsorbed on aluminium salts. It also contains three types of inactivated polio viruses (type 1: Mahoney strain; type 2: MEF-1 strain; type 3: Saukett strain).

The diphtheria and tetanus toxoids are obtained by formaldehyde treatment of purified *Corynebacterium diphtheriae* and *Clostridium tetani* toxins. The acellular pertussis vaccine components are obtained by extraction and purification from phase I *Bordetella pertussis* cultures, followed by irreversible detoxification of the pertussis toxin by glutaraldehyde and formaldehyde treatment, and formaldehyde treatment of FHA and PRN. The diphtheria toxoid, tetanus toxoid and acellular pertussis components are adsorbed onto aluminium salts.

The surface antigen of the HBV (HBsAg) is produced by culture of genetically-engineered *Saccharomyces cerevisiae* yeast cells which carry the gene coding for the major surface antigen of the HBV. This HBsAg expressed in yeast cells is purified by several physico-chemical steps.

The three polioviruses are cultivated on a continuous VERO cell line, purified and inactivated with formaldehyde.

A 0.5 mL dose of vaccine contains 30IU (25 Lf U) of diphtheria toxoid, 40IU (10 Lf U) of tetanus toxoid, 25µg of adsorbed PT, 25µg of adsorbed pertussis FHA, 8µg of adsorbed PRN, 10µg of adsorbed recombinant HBsAg protein, 40 D-antigen units of type 1 (Mahoney), 8 D-antigen units of type 2 (MEF-1) and 32 D-antigen units of type 3 (Saukett) of the polio virus. The final vaccine is formulated in saline and contains 2-phenoxyethanol.

The manufacture of this product includes exposure to bovine derived materials. No evidence exists that any case of vCJD (considered to be the human form of bovine spongiform encephalopathy) has resulted from the administration of any vaccine product.

INFANRIX PENTA meets the World Health Organisation requirements for manufacture of biological substances, of diphtheria, tetanus, pertussis and combined vaccines, of hepatitis B vaccines made by recombinant DNA techniques and of inactivated poliomyelitis vaccines.

CLINICAL PHARMACOLOGY

Clinical Trials

Primary Immunisation - Immunogenicity Studies

The immunogenicity of INFANRIX PENTA has been evaluated in >2400 infants during clinical trials. In these studies, INFANRIX PENTA was shown to induce antibodies against all of the components contained in the vaccine. The immunogenicity of INFANRIX PENTA was comparable to DTPa, Hepatitis B and OPV or IPV vaccines administered separately. A variety of primary vaccination schedules were used including vaccination at 2, 4 and 6 months (n= 681) and at 3, 4 and 5 months (n= 856). Immune responses from a pivotal clinical study that used a 2, 4, 6 month schedule are presented in the following table.

Immune responses one month following primary vaccination with INFANRIX PENTA vaccine at 2, 4, 6 months of age

Antigens (n)	Antibody Response (% Seropositive)	GMT (95% confidence intervals)
Diphtheria Toxoid (n= 328)	99.7	1.0 IU/mL (1.0-1.2)
Tetanus Toxoid (n= 328)	100	2.7 IU/mL (2.5-2.9)
Hepatitis B (n= 328)	99.1	1681.5 mIU/mL (1428.2 –1979.6)
Pertussis Toxoid (n= 328)	100	99.1 EL.U/mL (92.6-106.1)
Pertussis FHA (n= 303)	100	167.7 EL.U/mL (158.7-177.3)
Pertactin (n=328)	100	111.8 EL.U/mL (102.1-122.4)
Poliovirus Type 1 (n=326)	100	327.7 (291.7-368.2)
Poliovirus Type 2 (n=326)	100	319.1 (283.6-359.0)
Poliovirus Type 3 (n=325)	100	895.2 (793.2-1010.2)

IU = International Units; EL.U = ELISA Units.

The cut-off values for diphtheria and tetanus (≥0.1 IU/mL), hepatitis B (≥10 mIU/mL), and the three poliovirus serotypes (≥8) correlate with seroprotection.

The results for poliovirus are expressed as a titre which is the reciprocal of the highest dilution of serum showing 50% virus neutralisation effect in a microneutralisation test.

Currently there are no known serological correlates for protection for the pertussis antigens. The assay cutoff used for the pertussis antigens is (≥5 EL.U/mL).

Protective efficacy against pertussis following primary immunisation - INFANRIX® (DTPa)

The protective efficacy of INFANRIX (DTPa) following primary immunisation has been established using WHO-defined typical pertussis (≥21 days of paroxysmal cough with laboratory confirmation) in two clinical studies.

In a prospective blinded household contact study conducted in Germany, data was collected from 360 evaluable secondary contacts in households where there was an index case of typical pertussis. Vaccine efficacy was calculated at 88.7% with a two sided 95% confidence interval of 76.6% to 94.5%. This was not statistically different from the DTPw vaccine.

In a randomised, double-blind, controlled clinical study conducted in Italy, infants were administered three doses of INFANRIX at 2, 4 and 6 months of age, and followed for an average of 17 months (n=5951). INFANRIX vaccine efficacy was calculated to be 83.9% with a two sided 95% confidence interval of 75.8% to 89.4% against pertussis.

In a follow-up of the same cohort, the efficacy for INFANRIX vaccine was found to be 84% up to four years of age.

INFANRIX (DTPa) is an integral part of the INFANRIX PENTA combination vaccine. It is therefore expected that INFANRIX PENTA will provide similar protective efficacy.

Booster Dosing - following primary INFANRIX PENTA vaccination

The response of a booster dose of INFANRIX PENTA has been evaluated in 182 children aged 11 to 28 months who had previously received a primary vaccination course of INFANRIX PENTA. Data from such a study that administered a booster dose at 16-18 months of age are presented in the following table.

Immune responses one month following administration of INFANRIX PENTA vaccine as a booster dose in children aged 16-18 months

Antigen (n)	Antibody Response (% Seropositive)		GMT (95% confidence interval)	
	Pre-booster	Post-booster	Pre-booster	Post-booster
Diphtheria Toxoid (n=42)	64.3	100	0.2 IU/mL (0.1-0.3)	8.1 IU/mL (6.4-10.2)
Tetanus Toxoid (n=42)	92.9	100	0.3 IU/mL (0.3-0.5)	7.6 (5.7-10.1)
Hepatitis B (n=42)	92.9	100	108 (65-180)	6736 (4231-10724)
Pertussis Toxoid (n=42)	76.2	100	7.5 (6.0-9.2)	130.3 (110.5-153.8)
Pertussis FHA (n=40)	95.0	100	34.2 (26.0-45.0)	638.7 (535.3-762.0)
Pertactin (n=42)	81.0	100	13.3 (9.6-18.4)	381.0 (302.8-479.4)
Poliovirus Type 1 (n=41)	78.0	100	26.2 (16.2-42.5)	1264.0 (815.9-1958.0)
Poliovirus Type 2 (n=41)	90.2	100	38.4 (25.1-58.7)	1979.1 (1340.5-2922.0)
Poliovirus Type 3 (n=41)	95.1	100	163.4 (102.1-261.4)	4197.2 (3304.8-5330.5)

IU = International Units; EL.U = ELISA Units.
The cut-off values for diphtheria and tetanus (≥0.1 IU/mL), hepatitis B (≥10 mIU/mL), and the three poliovirus serotypes (≥8) correlate with seroprotection.
The results for poliovirus are expressed as a titre which is the reciprocal of the highest dilution of serum showing 50% virus neutralisation effect in a microneutralisation test.
Currently there are no known serological correlates for protection for the pertussis antigens. The cutoff value used for the pertussis antigens is (≥5 EL.U/mL)

INDICATIONS

INFANRIX PENTA is indicated for immunisation of infants from the age of 6 weeks against diphtheria, tetanus, pertussis, hepatitis B and poliomyelitis.

INFANRIX PENTA may also be used as a booster dose at 18 months of age if boosting with hepatitis B and poliomyelitis, as well as diphtheria, tetanus, and pertussis is required.

CONTRAINDICATIONS

INFANRIX PENTA should not be administered to subjects with known hypersensitivity to any component of the vaccine, or to subjects having shown signs of hypersensitivity after previous administration of diphtheria, tetanus, pertussis, hepatitis B or polio vaccines.

INFANRIX PENTA is contraindicated if the child has experienced an encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis containing vaccine. In these circumstances pertussis vaccination should be discontinued and the vaccination should be continued with diphtheria-tetanus, hepatitis B and polio vaccines.

PRECAUTIONS

INFANRIX PENTA should under no circumstances be administered intravenously.

It is good clinical practice that immunisation should be preceded by a review of the medical history (especially with regard to previous immunisation and possible occurrence of undesirable events) and a clinical examination.

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic reaction following the administration of the vaccine.

If any of the following events are known to have occurred in temporal relation to receipt of whole cell or acellular pertussis-containing vaccine, the decision to give further doses of vaccine containing the pertussis component should be carefully considered. No data currently exist on use of INFANRIX PENTA in these children. There may be circumstances, such as a high incidence of pertussis, when the potential benefits outweigh possible risks, particularly since these events are not associated with permanent sequelae.

- Temperature of ≥40.5°C within 48 hours, not due to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours.
- Persistent, inconsolable crying lasting ≥ 3 hours, occurring within 48 hours.
- Convulsions with or without fever, occurring within 3 days.

A history of febrile convulsions, a family history of convulsions, a family history of Sudden Infant Death Syndrome (SIDS) and a family history of an adverse event following INFANRIX PENTA vaccination do not constitute contra-indications.

As with other vaccines, the administration of INFANRIX PENTA should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection, however, is not a contraindication.

INFANRIX PENTA should be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration to these subjects.

INFANRIX PENTA should not be administered at birth. Infants born of HBsAg positive mothers should receive Hepatitis B immune globulin and Hepatitis B vaccine at birth. Only limited data exists on subsequent immunisation of these infants with INFANRIX PENTA

INFANRIX PENTA contains traces of neomycin and polymyxin. The vaccine should be used with caution in patients with known hypersensitivity to one of these antibiotics.

Human Immunodeficiency Virus (HIV) infection is not considered as a contra-indication. However in patients with immunodeficiency or in patients receiving immunosuppressive therapy, the expected immunologic response may not be achieved. No data currently exist on use of INFANRIX PENTA in these patients.

The vaccine will not prevent infection caused by other agents such as hepatitis A, hepatitis C and hepatitis E and other pathogens known to infect the liver.

As hepatitis D (caused by the delta agent) does not occur in the absence of hepatitis B infection, it can be expected that hepatitis D will also be prevented by vaccination with INFANRIX PENTA.

Use In Pregnancy (Category B2)

INFANRIX PENTA is not indicated or recommended for use in pregnant women, and has not been evaluated for potential harmful effects during pregnancy in animals or humans.

Use In Lactation

INFANRIX PENTA is not indicated or recommended for use in lactating women, and it is not known whether INFANRIX PENTA is transferred in human or animal milk.

Interactions

Clinical studies have demonstrated that INFANRIX PENTA can be administered simultaneously with *Haemophilus influenzae* type b vaccines. In these clinical studies, the injectable vaccines were given at different injection sites.

INFANRIX PENTA should not be mixed with other vaccines in the same syringe.

ADVERSE REACTIONS

Clinical Trial Experience

INFANRIX PENTA has been assessed for safety and reactogenicity in controlled clinical trials in over 7000 infants. Diary cards were used to actively monitor signs and symptoms following vaccination.

Primary Immunisation

In a large clinical study involving more than 3000 subjects, the following solicited symptoms were reported during the first four days after vaccination. Virtually all symptoms reported resolved within four days and all subjects recovered without sequelae. A causal relationship between vaccine use and the recorded event has not been established for each individual event.

Incidence (%) of solicited symptoms following immunisation with INFANRIX PENTA at 3, 4, and 5 months

Solicited Symptoms	% incidence (N = 9032)
Local Reactions	
Pain at the injection site	11.6
Redness (>20mm)	1.1
Swelling (>20mm)	1.5
General Symptoms	
Fever ≥38.0°C	20.0
>39.5°C	0.5
Loss of appetite	14.3
Restlessness	34.3
Unusual crying	12.9
Vomiting	7.6
Diarrhoea	10.9

N = Total number of doses administered

The incidence of solicited symptoms following vaccination with INFANRIX PENTA was compared to separate administration of INFANRIX, Hepatitis B, and either oral or inactivated injectable polio vaccine. No significant difference in the frequency of solicited symptoms was observed between the INFANRIX PENTA group and the comparator groups. Virtually all symptoms reported resolved within four days and all subjects recovered without sequelae. A causal relationship between vaccine use and the recorded event has not been established for each individual event.

Incidence (%) of solicited symptoms observed in a comparative clinical study using a 2, 4, 6 month schedule.

Solicited Symptoms	INFANRIX PENTA % (N=291)	INFANRIX-HepB +IPV % (N=278)		INFANRIX + Engerix B + OPV % (N=269)	
Local Reactions		INFANRIX -HepB	IPV	INFANRIX	EngerixB
Pain at the injection site	27.8	27.3	22.3	25.3	20.4
Redness (>20mm)	1.0	0.4	0.0	0.0	0.0
Swelling (>20mm)	2.1	1.1	0.4	0.7	0.0
General Symptoms					
Fever (≥ 38.0°C)	19.2	15.5		14.1	
Fever (> 39.5°C)	1.0	0.0		0.7	
Loss of appetite	18.2	22.3		18.2	
Fussiness	55.0	61.2		53.9	
Unusual crying	2.1	2.5		2.2	
Sleeping less than usual	19.6	23.4		22.3	
Sleeping more than usual	33.3	34.2		34.2	
Vomiting	5.2	7.2		7.8	
Diarrhoea	11.0	9.4		14.9	

N = Total number of doses administered

No significant differences were found between the study groups with respect to the incidence of any of the individual symptoms.

Booster Immunisation

The table below summarises the incidence of solicited symptoms reported during the first four days following a booster dose of INFANRIX PENTA in over 300 children aged 12-28 months. The majority of symptoms were mild, and all subjects recovered without sequelae. A causal relationship between vaccine use and the recorded event has not been established for each individual event.

Incidence (%) of solicited symptoms from a study of booster immunisation following a 3, 4, 5 month primary schedule

Solicited Symptoms	% incidence (N = 359)
Local Reactions	
Pain at the injection site	28.1
Redness (>20mm)	5.0
Swelling (>20mm)	4.2
General Symptoms	
Fever >38.0°C	35.4
Fever >39.5°C	3.9
Loss of appetite	23.4
Restlessness	22.0
Fussiness	26.2
Vomiting	5.0
Diarrhoea	14.5
Sleepiness	19.5

N = Total number of doses administered

Other events

The following unsolicited events have been reported in clinical trials. It should be noted that causality has not necessarily been established for these events.

Events are listed within body systems and categorised by frequency according to the following definitions: *very common* events reported at a frequency of greater or equal to 1/10 patients; *common* events reported at a frequency of less than 1/10 but greater or equal to 1/100 patients; *uncommon* events reported at a frequency of less than 1/100 but greater or equal to 1/1,000 patients; *rare* events reported at a frequency of less than 1/1,000 patients but greater or equal to 1/10,000 patients; *very rare* events reported at a frequency of less than 1/10,000 patients.

Injection site: ***Very common:* local swelling at the injection site ≤ 50mm***
Common: injection site mass, **local swelling at the injection site >50mm***
Uncommon:* diffuse swelling of the injected limb, sometimes involving the adjacent joint

***Children primed with acellular pertussis vaccines are more likely to experience swelling reactions after booster administration in comparison with children primed with whole cell vaccines. These reactions resolve over an average of 4 days.**

Body as a whole: *Common*: fatigue

Central Nervous System: *Common*: nervousness

Resistance Mechanism: *Common*: viral infection, otitis media, upper respiratory tract infection
Respiratory System: *Common*: bronchitis, rhinitis

As for other DTPa vaccines, a slight increase in reactogenicity was reported after booster vaccination, with a low incidence of symptoms graded as severe.

Allergic reactions including anaphylactoid reactions may occur very rarely following vaccination with INFANRIX combination vaccines.

Post-marketing Experience
Post-marketing experience is currently limited.

Very rare cases of collapse or shock-like state (hypotonic-hyporesponsiveness episode) and convulsions within 2 to 3 days of vaccination have been reported in subjects who received INFANRIX alone. All the subjects recovered without sequelae.

Swelling of the entire injected limb has been observed very rarely during post-marketing surveillance.

DOSAGE AND ADMINISTRATION

All parenteral drug and vaccine products should be inspected visually for any particulate matter or discolouration prior to administration. Before use of INFANRIX PENTA, the vaccine should be well shaken to obtain a homogenous turbid suspension. Discard the vaccine if it appears otherwise. The vaccine should be administered immediately after opening.

Dosage
Each dose consists of a 0.5mL ready to use sterile suspension.

Administration
INFANRIX PENTA is administered by intramuscular injection. THE VACCINE SHOULD NEVER BE ADMINISTERED INTRAVENOUSLY.

INFANRIX PENTA should be injected intramuscularly in the anterolateral aspect of the thigh or the deltoid region of the arm. The recommended dose (0.5mL) of vaccine must be administered.

Immunisation Schedule
The primary vaccination course consists of three doses. INFANRIX PENTA is recommended for administration at 2, 4 and 6 months of age.

INFANRIX PENTA can be given as a booster dose at 18 months if boosting with Hepatitis B and/or poliovirus, as well as diphtheria, tetanus and pertussis is required. For example, this may be appropriate for some children who need a booster dose of Hepatitis B following an accelerated immunisation (such as 3 doses at 1 month intervals) with Hepatitis B vaccine. There is no theoretical concern regarding receipt of an additional dose of Hepatitis B or inactivated poliovirus vaccine.

STORAGE

INFANRIX PENTA should be stored between +2°C and +8°C. DO NOT FREEZE. Discard if vaccine has been frozen. Protect from light.

The expiry date of the vaccine is indicated on the label and packaging.

PRESENTATIONS

INFANRIX PENTA is presented as a turbid white suspension in a prefilled syringe or in a vial*. Upon storage, a white deposit and clear supernatant can be observed.

The syringes and vials are made of neutral glass type I, which conforms to European Pharmacopoeia Requirements.

MANUFACTURER:

GlaxoSmithKline Biologicals sa
Rue de l'Institut 89
1330 Rixensart, Belgium.

DISTRIBUTED IN AUSTRALIA BY:

GlaxoSmithKline Australia Pty Ltd
1061 Mountain Highway
Boronia VIC 3155

Date of TGA Approval: **TBA**

Issue 3

® INFANRIX is a registered trade mark of the GlaxoSmithKline group of companies

*** The vial presentation is not currently marketed in Australia.**

INFANRIX-IPV Product Information

INFANRIX® IPV

NAME OF THE DRUG

INFANRIX® IPV vaccine is a combined diphtheria, tetanus, acellular pertussis (DTPa) and inactivated poliovirus vaccine.

DESCRIPTION

INFANRIX® IPV vaccine is a sterile suspension which contains diphtheria toxoid (D), tetanus toxoid (T), three purified antigens of *Bordetella pertussis* [pertussis toxoid (PT), pertussis filamentous haemagglutinin (FHA) and pertussis 69 kilodalton outer membrane protein (69kDa OMP) (pertactin)] and three types of inactivated polio viruses (type 1: Mahoney strain; type 2: MEF-1 strain; type 3: Saukett strain).

The diphtheria and tetanus toxoids are obtained by formaldehyde treatment of purified *Corynebacterium diphtheriae* and *Clostridium tetani* toxins. The acellular pertussis vaccine components are obtained by extraction and purification from phase I *Bordetella pertussis* cultures, followed by irreversible detoxification of the pertussis toxin by glutaraldehyde and formaldehyde treatment, and formaldehyde treatment of FHA and pertactin. The three polioviruses are cultivated on a continuous VERO cell line, purified and inactivated with formaldehyde.

A 0.5mL dose of vaccine contains not less than 30IU (25Lf U) of diphtheria toxoid, not less than 40IU (10Lf U) of tetanus toxoid, 25µg of adsorbed PT, 25µg of adsorbed pertussis FHA, 8µg of adsorbed pertactin, 40 D-antigen units of type 1 (Mahoney), 8 D-antigen units of type 2 (MEF-1) and 32 D-antigen units of type 3 (Saukett) polioviruses. The final vaccine is formulated in saline and contains phenoxyethanol as preservative.

The manufacture of this product includes exposure to bovine derived materials. No evidence exists that any case of vCJD (considered to be the human form of bovine spongiform encephalopathy) has resulted from the administration of any vaccine product.

INFANRIX® IPV vaccine meets the World Health Organisation requirements for manufacture of biological substances, of diphtheria, tetanus, pertussis and combined vaccines, and of inactivated poliomyelitis vaccines.

PHARMACOLOGY

Clinical Trials

More than 1,800 doses of *INFANRIX® IPV* have been administered in clinical studies evaluating use in primary vaccination schedules. In addition, 608 doses have been administered as a single booster dose in infants and children ranging from 15 months to 13 years.

Immune response to the DT components:

One month after a 3 dose primary vaccination course with *INFANRIX® IPV*, more than 99% of vaccinated infants had antibody titres of ≥ 0.1 IU/mL to both tetanus and diphtheria.

Following administration of a booster dose of *INFANRIX® IPV*, more than 99.5% of children had antibody titres of≥ 0.1 IU/mL for both antigens.

Antibody titres ≥ 0.1IU/mL are deemed to correlate with seroprotection against diphtheria and tetanus.

Immune response to the Pa component:

One month after the 3-dose primary vaccination course with *INFANRIX® IPV*, 100% of infants were seropositive (antibodies ≥5 EL.U/mL) for the three pertussis components (PT, FHA, pertactin). Overall response rates, for each of the three individual pertussis antigens were ≥ 94%. A vaccine response was defined as induction of antibodies to the individual pertussis antigens, taking into account the age and the pre-vaccination serological status of the subject.

In booster studies, a vaccine response was seen in ≥96.6% of vaccinees against the pertussis antigens; lower response rates were seen in studies where the pre-vaccination levels of antibodies were high. A vaccine response was defined as a post-vaccination titre ≥ 2x the pre-vaccination titre for subjects initially seropositive, and a titre ≥ the assay cut-off (5 EL.U/ml) for subjects initially seronegative. All subjects were seropositive one month after this dose.

Protective efficacy of the Pa component:

As the immune response to pertussis antigens following *INFANRIX® IPV* administration is equivalent to that of *INFANRIX®*, it can be assumed that the protective efficacy of the two vaccines will also be equivalent.

The clinical protection of the DTPa component, against WHO-defined typical pertussis (≥ 21 days of paroxysmal cough) was demonstrated in:

- a prospective blinded household contact study was performed in Germany (3, 4, 5 months schedule). Based on data collected from secondary contacts in households where there was an index case with typical pertussis, the protective efficacy of the vaccine was calculated to be 88.7%.

- a US National Institute of Health (NIH) sponsored efficacy study was performed in Italy (2, 4, 6 months schedule). This study determined the vaccine efficacy to be 84%. In a follow-up of the same cohort, the efficacy was confirmed for up to 4 years of age.

Immune response to the IPV component:

One month after the 3 dose primary vaccination course with *INFANRIX® IPV*, the overall seropositivity for each of the three polio serotypes (type 1, 2 and 3) was ≥ 99.5%. Antibody titres ≥8 are deemed to correlate with seroprotection against poliomyelitis.

Following administration of a booster dose of *INFANRIX® IPV*, 100% of children were seropositive for the three polio serotypes.

In all booster trials, vaccination with *INFANRIX® IPV* induced a marked increase in antibody levels with respect to pre-booster values.

Geometric Mean Antibody Titres (GMTs) following primary immunisation with INFANRIX® IPV vaccine in children at 7 months of age

Antigen	Primary immunisation GMT [95% confidence interval]
Diphtheria Toxoid (N=203)	1.83 [1.69 – 1.98]
Tetanus Toxoid (N=193)	3.72 [3.47 – 3.99]
Pertussis Toxoid (N=198)	87.2 [81.7 – 93.0]
Pertussis FHA (N=188)	91.1 [80.6 – 102.9]
Pertactin (N=188)	166.6 [151.6 – 183.1]
Poliovirus Type 1 (N=174)	374.5 [326.8 – 429.1]
Poliovirus Type 2 (N=175)	406.1 [352.9 – 467.2]
Poliovirus Type 3 (N=175)	1115.0 [978.4 – 1270.6]

Note: Primary immunisation with DTPa-IPV vaccine at 3, 4.5, 6 months

IU = International Units; EL.U = ELISA Units; N = Number of subjects
Assay cut-offs for each antigen are as follows: D & T: ≥0.1IU/mL; PT, FHA & PRN: 5EL.U/mL; POLIO types 1,2,3: ≥8.
The cut-off values for diphtheria, tetanus and polio correlate with seroprotection. Currently there are no known serological correlates for protection for the pertussis antigens.

Geometric Mean Antibody Titres (GMT) following booster immunisation with INFANRIX® IPV at 21 months of age

Antigen	Booster immunisation GMT [95% confidence interval]	
	Pre-booster	Post-booster
Diphtheria Toxoid (N=37)	0.124 [0.096 – 0.158]	2.610 [1.836 – 3.713]
Tetanus Toxoid (N=37)	0.306 [0.243 – 0.385]	6.331 [4.808 - 8.335]
Pertussis Toxoid (N=37)	7.0 [5.0 – 9.7]	179.6 [133.3 – 242.0]
Pertussis FHA (N=37)	17.8 [13.4 – 23.7]	340.3 [258.3 – 448.2]
Pertactin (N=37)	18.2 [14.2 – 23.4]	429.9 [311.0 – 594.4]
Poliovirus Type 1 (N=34 [pre] and 36 [post])	138.9 [87.2 – 221.2]	3577.3 [2481.4 – 5157.3]
Poliovirus Type 2 (N=34 [pre] and 36 [post])	181.1 [112.3 – 291.9]	2868.3 [1781.9 – 4616.9]
Poliovirus Type 3 (N=34 [pre] and 36 [post])	286.3 [181.3 – 452.2]	5358.8 [3693.0 – 7776.0]

Note: Primary immunisation with DTPa-IPV vaccine
IU = International Units; EL.U = ELISA Units; N = Number of subjects
Assay cut-offs for each antigen are as follows: D & T: ≥0.1IU/mL; PT, FHA & PRN: 5EL.U/mL; POLIO types 1,2,3: ≥8.
The cut-off values for diphtheria, tetanus and polio correlate with seroprotection. Currently there are no known serological correlates for protection for the pertussis antigens.

Geometric Mean Antibody Titres (GMTs) from a study of booster immunisation with INFANRIX® IPV at 5-6 years of age, following primary and first booster immunisation

Antigen	Booster immunisation GMT (95% confidence interval)	
	Pre-booster	Post-booster
Diphtheria Toxoid (N=72 [pre] and 73 [post])	0.12 (0.09 – 0.15)	6.19 (4.83 – 7.93)
Tetanus Toxoid (N=72 [pre] and 73 [post])	0.25 (0.20 – 0.32)	13.58 (11.30 – 16.31)
Pertussis Toxoid (N=72 [pre] and 66 [post])	3.6 (3.0 – 4.3)	84.7 (62.5 – 114.9)
Pertussis FHA (N=70 [pre] and 72 [post])	31.8 (22.1 – 45.9)	1051.1 (898.3 – 1299.8)
Pertactin (N=72 [pre] and 73 [post])	16.8 (12.7 – 22.3)	820.1 (656.8 – 1024.0)
Poliovirus Type 1 (N=72)	15.6 (11.7 – 20.8)	1533.2 (1156.6 – 2032.2)
Poliovirus Type 2 (N=72 [pre] and 71 [post])	21.8 (16.3 – 29.0)	1053.4 (819.7 – 1353.6)
Poliovirus Type 3 (N=71)	44.4 (31.9 – 61.7)	1740.7 (1315.7 – 2303.0)

Note: Primary and first booster immunisation with DTPw-IPV or DTPw-IPV/Hib vaccine
N = Number of subjects; IU = International Units; EL.U = ELISA Units
Assay cut-offs for each antigen are as follows: D & T: ≥0.1IU/mL; PT, FHA & PRN: 5EL.U/mL; POLIO types 1,2,3: ≥8.
The cut-off values for diphtheria, tetanus and polio correlate with seroprotection. Currently there are no known serological correlates for protection for the pertussis antigens.

INDICATIONS

INFANRIX® IPV is indicated for use in a three dose primary schedule for immunisation of infants from 6 weeks of age and over, against diphtheria, tetanus, pertussis and poliomyelitis.

INFANRIX® IPV is also indicated as a single booster dose for children, up to and including 6 years of age, who have previously been immunised against DTP and polio.

CONTRAINDICATIONS

INFANRIX® IPV is contraindicated after an immediate anaphylactic reaction temporally related to a previous dose of the vaccine.

INFANRIX® IPV should not be administered to subjects having shown signs of hypersensitivity after previous administration of diphtheria, tetanus, pertussis, or inactivated polio vaccines.

INFANRIX® IPV is contraindicated if the child has experienced an encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with a pertussis containing vaccine. In these circumstances pertussis vaccination should be discontinued and the vaccination should be continued with diphtheria-tetanus and polio vaccines.

PRECAUTIONS

***INFANRIX® IPV* should under no circumstances be administered intravenously.**

It is good clinical practice that immunisation should be preceded by a review of the medical history (especially with regard to previous immunisation and possible occurrence of undesirable events) and a clinical examination.

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic reaction following the administration of the vaccine.

If any of the following events are known to have occurred in temporal relation to receipt of whole cell or acellular pertussis-containing vaccine, the decision to give further doses of vaccine containing the pertussis component should be carefully considered. There may be circumstances, such as a high incidence of pertussis, when the potential benefits of vaccination outweigh the possible risks, particularly since these events are not associated with permanent sequelae.

- Temperature of ≥40.5°C within 48 hours, not due to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours.
- Persistent, inconsolable crying lasting ≥ 3 hours, occurring within 48 hours.
- Convulsions with or without fever, occurring within 3 days.

A history of febrile convulsions, a family history of convulsions, a family history of Sudden Infant Death Syndrome (SIDS) or a family history of an adverse event following DTPa and/or IPV vaccination do not constitute contra-indications.

As with other vaccines, the administration of *INFANRIX® IPV* should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection, however, is not a contraindication.

INFANRIX® IPV should be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration to these subjects. Firm pressure should be applied to the injection site (without rubbing) for at least two minutes.

INFANRIX® IPV contains traces of neomycin sulfate and polymyxin sulfate. The vaccine should be used with caution in patients with known hypersensitivity to one of these antibiotics.

Human Immunodeficiency Virus (HIV) infection is not considered a contra-indication to *INFANRIX® IPV* vaccination. However in patients with immunodeficiency or in patients receiving immunosuppressive therapy, the expected immunologic response may not be achieved. No data currently exist on use of *INFANRIX® IPV* in these patients.

Use During Pregnancy:
Adequate human data on use during pregnancy and adequate animal reproduction studies are not available.

Use During Lactation:
Adequate human data on use during lactation and adequate animal reproduction studies are not available.

Interactions with other drugs

It is current practice in paediatric vaccination to co-administer different vaccines during the same session. Injectable vaccines should always be given at different injection sites.

INFANRIX® IPV can be administered concomitantly with hepatitis B vaccine, and/or *Haemophilus influenzae* type b vaccine, the injections being administered at different injection sites. Routine simultaneous administration of Hib vaccine and hepatitis B

vaccine may be performed for children who are at the recommended age to receive these vaccines.

Concomitant administration of *INFANRIX® IPV* and the PRP-OMP type Hib vaccine, measles, mumps and rubella combined vaccine, and varicella vaccine has not been assessed in clinical studies. The Australian Immunisation Handbook 2000 accepts that these vaccines may be given at the same time if separate injection sites are used.

INFANRIX® IPV should not be mixed with other vaccines in the same syringe.

ADVERSE REACTIONS

Clinical Trial Experience

Adverse reactions associated with *INFANRIX® IPV* vaccination have been evaluated in 13 clinical trials, with more than 2,400 doses administered. Adverse event data were actively collected using diary cards and by questioning the parents at clinic visits.

Primary vaccination with *INFANRIX® IPV*

Incidence (%) of general solicited symptoms reported within 48 hours following primary immunisation of infants with INFANRIX® IPV at a 3, 4.5, 6 month schedule

Solicited Symptoms	% incidence (N = 726)
Local Reactions:	
Pain at the injection site	16.3
Redness (>20mm)	4.4
Swelling (>20mm)	3.4
General Symptoms:	
Fever:	
Any#	6.1
Grade 3@	0.1
Loss of appetite	10.7
Restlessness	22.7
Unusual crying	18.2
Vomiting	6.5
Diarrhoea	11.6

N = Total number of doses administered over a 3 dose primary vaccination course
 # = A temperature of ≥37.5°C (axillary or oral) or ≥38°C (rectal)
@ = A temperature of >39°C (axillary or oral) or >39.5°C (rectal)

The following events were also reported in temporal association with vaccination in clinical trials evaluating the 3 dose primary vaccination schedules. It should be noted that causality has not necessarily been established for these events.

Events are listed within body systems and categorised by frequency according to the following definitions: *common* events reported at a frequency of greater or equal to 1/100 patients; *uncommon* events reported at a frequency of less than 1/100 but greater or equal to 1/1,000 patients; *rare* events reported at a frequency of less than 1/1,000 patients.

Body as a whole: *Uncommon:* bacterial infection, fungal injection, viral infection, herpes zoster (chicken pox), moniliasis

Cardiovascular: *Uncommon:* haematoma

Central Nervous System: *Common:* Somnolence

Dermatological: *Uncommon:* rash, dermatitis, dermititis contact, eczema, rash erythematous

Gastrointestinal: *Common:* tooth ache; *Uncommon:* dyspepsia, hiccup, abdominal pain, gastroenteritis, gastro-oesophageal reflux, constipation, flatulence

Injection site:

Common: injection site mass

Nervous System: *Uncommon:* insomnia

Respiratory: *Common:* rhinitis, pharyngitis, upper respiratory tract infection

Uncommon: asthma, coughing, pneumonia, respiratory disorder, bronchitis

Special senses: *Common:* otitis media; *Uncommon:* conjunctivitis

Urogenital: *Uncommon:* pyelonephritis

Booster vaccination with *INFANRIX® IPV* at 5-6 years of age

Incidence (%) of solicited symptoms reported within 48 hours *from a study of booster immunisation with INFANRIX® IPV at 5-6 years of age following primary and first booster immunisation*

Solicited Symptoms	% incidence (*N = 73)
Local Reactions:	
Pain at the injection site:	
Any	82.2
Grade 3	5.5
Redness:	
Any	65.8
>50mm	9.6
Swelling:	
Any	52.1
>50mm	5.5
General Symptoms:	
Fever:	
Any#	9.6
Grade 3@	0.0
Irritability	13.7
Vomiting	1.4
Diarrhoea	2.7
Loss of appetite	12.3
Restlessness	6.8
Sleeping more than usual	17.8

Note: Primary and first booster immunisation with DTPw-IPV or DTPw-IPV/Hib vaccine
**N =Number of subjects*
 # = A temperature of ≥37.5°C (axillary or oral) or ≥38°C (rectal)
@ = A temperature of >39°C (axillary or oral) or >39.5°C (rectal)

The following events were also reported in temporal association with vaccination in clinical trials evaluating booster vaccination schedules. It should be noted that causality has not necessarily been established for these events.

Events are listed within body systems and categorised by frequency according to the following definitions: ***very common* events reported at a frequency of greater or equal to 1/10 patients;** *common* events reported at a frequency of **less than 1/10 but** greater or equal to 1/100 patients; *uncommon* events reported at a frequency of less than 1/100 but greater or equal to 1/1,000 patients; *rare* events reported at a frequency of less than 1/1,000 **but greater or equal to 1/10,000 patients; *very rare* events reported at a frequency of less than 1/10,000** patients.

Injection site: Very common: local swelling at the injection site (≤ 50 mm)*
Common:* local swelling at the injection site (>50 mm)
Uncommon:* diffuse swelling of the injected limb, sometimes involving the adjacent joint

Body as a whole: *Common:* asthenia; *Uncommon:* viral infection
Dermatological: *Common:* pruritis
Gastrointestinal: *Uncommon:* abdominal pain
Musculoskeletal: *Uncommon:* myalgia
Respiratory: *Common:* coughing, rhinitis, pharyngitis; *Uncommon:* bronchitis
Special senses: *Common:* otitis media

***Children primed with acellular pertussis vaccines are more likely to experience swelling reactions after booster administration in comparison with children primed with whole cell vaccines. Local swelling at the injection site (>50 mm) and diffuse swelling may be more frequent (very common and common, respectively) when the booster dose is administered between 4 and 6 years. These reactions resolve over an average of 4 days.**

~~Large oedematous swelling leading to an increased circumference of the injected limb has been observed in clinical trial studies of booster doses of INFANRIX®, with an incidence of approximately 1%. This is consistent with the reported incidences of extensive swelling of 1 – 2.7% following booster doses of various DTPa vaccines.~~

Post-marketing Experience

~~Post marketing experience with *INFANRIX® IPV* is currently limited.~~

Very rare allergic reactions, including anaphylactoid reactions, have been reported following vaccination with DTPa containing vaccines.

Extremely rare cases of collapse or shock-like state (hypotonic-hyporesponsiveness episode) and convulsions within 2 to 3 days of vaccination have been reported for infants receiving pertussis-containing vaccines. All the subjects recovered totally without sequelae.

Very rare swelling of the entire injected limb has been reported.

~~Large oedematous swelling has been reported very rarely with booster dose administration of *INFANRIX® IPV*. In post-marketing experience with *INFANRIX®*, large oedematous swelling has been reported very rarely and most frequently after booster doses but may also occur following doses in the primary series. Cases of large~~

oedematous swelling generally begin within 48 hours of vaccination and resolve over an average of 4 days without sequelae.

DOSAGE AND ADMINISTRATION

All parenteral drug and vaccine products should be inspected visually for any particulate matter or discolouration prior to administration. Before use of *INFANRIX® IPV*, the vaccine should be well shaken to obtain a homogenous turbid suspension. Discard the vaccine if it appears otherwise. The vaccine should be administered immediately after opening.

Dosage

Each dose consists of a 0.5mL ready to use sterile suspension.

Administration

INFANRIX® IPV is administered by deep intramuscular injection. For infants, the preferred site of injection is the anterolateral aspect of the thigh because of the small size of their deltoid muscle. In older children, the booster vaccination should be administered in the deltoid region of the arm. The recommended dose (0.5mL) of vaccine must be administered. Each dose of *INFANRIX® IPV* is for single use only. Any residual vaccine must be discarded.

INFANRIX® IPV VACCINE SHOULD NEVER BE ADMINISTERED INTRAVENOUSLY.

Immunisation Schedule

Primary

The primary vaccination course consists of three doses of *INFANRIX® IPV*. *INFANRIX® IPV* is recommended for administration at 2, 4 and 6 months of age. An interval of at least 1 month should be maintained between subsequent doses.

Booster

A single booster dose of *INFANRIX® IPV* can be given up to and including 6 years of age.

Storage

INFANRIX® IPV should be stored between +2°C and +8°C. DO NOT FREEZE. Discard if vaccine has been frozen. Protect from light.

The expiry date of the vaccine is indicated on the label and packaging.

PRESENTATIONS

INFANRIX® IPV is presented as a turbid white suspension in a prefilled syringe or vial*. Upon storage, a white deposit and clear supernatant can be observed.

The syringes and vials are made of neutral glass type I, which conforms to European Pharmacopoeia Requirements

MANUFACTURER

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
1330 Rixensart, Belgium.

DISTRIBUTED IN AUSTRALIA BY

GlaxoSmithKline Australia Pty. Ltd.
1061 Mountain Highway
Boronia VIC 3155

Date of TGA Approval: ~~17 July 2002~~**TBA**
~~Date of last amendment: 12 November 2003~~

Issue 3

* The vial presentation is not currently marketed in Australia.

®*INFANRIX* is a registered trademark of the GlaxoSmithKline group of companies.

INFANRIX Product Information

INFANRIX® PRODUCT INFORMATION

Diphtheria-tetanus-acellular pertussis (DTPa) vaccine

DESCRIPTION

INFANRIX DTPa vaccine is a sterile suspension which contains diphtheria toxoid, tetanus toxoid and three purified antigens of *Bordetella pertussis* [pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN)] adsorbed onto aluminium hydroxide.

The diphtheria and tetanus toxins are obtained from cultures of *Corynebacterium diphtheriae* and *Clostridium tetani* and are then detoxified and purified. The acellular pertussis vaccine components (PT, FHA and PRN) are extracted from phase I *Bordetella pertussis*, and are then purified and stabilised.

Each 0.5mL dose of INFANRIX contains not less than 30 IU of diphtheria toxoid, 40 IU of tetanus toxoid, 25 µg of PT, 25 µg of FHA and 8 µg of PRN. The diphtheria toxoid, tetanus toxoid and acellular pertussis vaccine (DTPa) components are adsorbed on 0.5mg aluminium in the form of aluminium hydroxide, and suspended in isotonic sodium chloride. The vaccine preparation also contains 2-phenoxyethanol as a preservative.

The manufacture of this product includes exposure to bovine derived materials. No evidence exists that any case of vCJD (considered to be the human form of bovine spongiform encephalopathy) has resulted from the administration of any vaccine product.

INFANRIX meets the World Health Organisation requirements for biological substances and for diphtheria and tetanus vaccines. No substances of human origin are used in its manufacture.

CLINICAL PHARMACOLOGY

INFANRIX DTPa vaccine, induces antibodies against all vaccine components.

Clinical Trials

Primary Immunisation - Protective Efficacy Studies

In a randomised, double-blind, controlled clinical study conducted in Italy, the efficacy of a primary vaccination course of INFANRIX against pertussis was assessed. Pertussis was defined as illness with paroxysmal cough of ≥21 days, and confirmation of *B. pertussis* infection by culture or serology. Infants were administered three vaccine doses at 2, 4, and 6 months of age, and followed for an average of 17 months. Of 4481 infants receiving 3 doses of INFANRIX, 37 confirmed cases of pertussis were reported. Of 1470 infants in the control group receiving 3 doses of diphtheria and tetanus antigens only, 74 confirmed cases of pertussis were reported. INFANRIX vaccine efficacy was calculated to be 83.9% with a two sided 95% confidence interval of 75.8% to 89.4%. Blood samples were collected from a 10% subset of children. Response to

diphtheria and tetanus antigens (antibody titre >0.1 IU/mL dose) was recorded in 96.6% and 99.8% respectively of this subset (>0.01 IU/mL is considered the minimum protective level).

A prospective blinded household contact study conducted in Germany assessed the vaccine efficacy (VE) of a primary course of INFANRIX against typical pertussis (defined by World Health Organization as spasmodic cough of ≥21 days, with confirmation of *B.pertussis* infection by culture or serology) up until the time of booster dosing. Of the 360 evaluable secondary contacts in households where there was an index case of typical pertussis, 173 were unvaccinated, 112 received INFANRIX, and 75 received a whole cell DTP vaccine. Of the 173 unvaccinated contacts, 96 developed typical pertussis, compared with 7 of the 112 contacts vaccinated with INFANRIX. The VE for INFANRIX was calculated at 88.7% with a two sided 95% confidence interval of 76.6% to 94.6%. Protection did not wane until at least the time recommended for booster vaccination.

Primary Immunisation - Immunogenicity Studies

The immunogenicity of primary vaccination schedules of INFANRIX have been evaluated in over 1700 infants administered the vaccine at either 2, 4, and 6 months (n=417) or 3, 4, and 5 months of age (n=1302). For the 2, 4, 6 month schedule, over 99% of vaccinees displayed antibody titres ≥0.1IU/mL for diphtheria and tetanus one month after the third dose. The pre and post GMT values for the three pertussis antigens are provided in the following table.

Antigen	N	GMT (EI.U/mL) pre	GMT (EI.U/mL) post #
PT	417	3.5	68
FHA	417	8.9	218
PRN	417	5.3	142

One month after the third vaccine dose

The overall response rates observed with INFANRIX for the diphtheria, tetanus, and three pertussis antigens, were equal or superior to those obtained after immunisation with a whole-cell DTP (DTPw) vaccine.

INFANRIX Booster Dosing - following primary DTPw vaccination

The response to INFANRIX booster doses after a primary DTPw vaccination course has been assessed in 559 children administered doses at 15-20 months (n=400) or at 3 to 7 years of age (n=159). Similar booster responses following the fourth at 15-20 months of age or fifth vaccine dose at 3-7 years of age, were observed for each of the vaccine antigens studied. Following the fourth vaccine dose, diphtheria and tetanus antibodies one month after vaccination were demonstrated in 94.0% and 99.3% of vaccinees respectively; compared to antibody responses of 99.4% and 98.1% respectively following the fifth vaccine dose. All vaccinees had antibody titres of

≥ 0.1 IU/mL against diphtheria and tetanus. The pre and post GMT values for the three pertussis antigens following a fourth or fifth vaccine dose are provided in the following tables. Overall the booster response following INFANRIX was equal or superior to that obtained following DTPw booster vaccination.

Antigen	15-20 months of age (N)	GMT (El.U/mL) pre-booster	GMT (El.U/mL) post-booster#
PT	400	7	136
FHA	382	7	232
PRN	396	9	376

One month after vaccination

Antigen	3-7 years of age (N)	GMT (El.U/mL) pre-booster	GMT (El.U/mL) post-booster#
PT	159	6	108
FHA	159	17	536
PRN	158	7	207

One month after vaccination

INFANRIX Booster Dosing - following primary INFANRIX (DTPa) vaccination

The response to INFANRIX booster doses after a primary DTPa vaccination course has been assessed in over 520 children administered a fourth dose between 15 and 24 months of age. No data are available on the use of INFANRIX as a fifth dose following primary and first booster (fourth dose) vaccination using DTPa, as the children studied had not yet reached an age to receive the final dose. A booster response to the diphtheria and tetanus antigens occurred in 97% and 100% of vaccinees respectively, one month after vaccination. All vaccinees had antibody titres of ≥ 0.1 IU/mL against diphtheria and tetanus, and 98% displayed antibody titres ≥ 1 IU/mL for both antigens. The pre and post GMT values for the three pertussis components are provided in the table below.

Antigen	15-24 months of age (N)	GMT (El.U/mL) pre-booster	GMT (El.U/mL) post-booster#
PT	174	8	93
FHA	167	37	502
PRN	174	18	631

One month after vaccination

INDICATIONS

INFANRIX (DTPa) is indicated for active primary immunisation against diphtheria, tetanus and pertussis when commenced between 2 months and 12 months of age.

INFANRIX (DTPa) is also indicated as fourth and fifth dose for children from 15 months of age up to and including 6 years of age who have been immunised previously with three or four doses of diphtheria, tetanus and pertussis (whole-cell or acellular) vaccine.

CONTRAINDICATIONS

INFANRIX should not be administered to subjects with known hypersensitivity to any components of the vaccine, and should not be administered to subjects having shown signs of hypersensitivity after previous administration of INFANRIX, diphtheria and tetanus vaccine and DTPw.

As with other vaccines, the administration of INFANRIX should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection, however, is not a contraindication.

INFANRIX is contraindicated if the child has experienced an encephalopathy occurring within 7 days following previous vaccination with pertussis containing vaccine

PRECAUTIONS

INFANRIX should under no circumstances be administered intravenously.

It is good clinical practice that immunisation should be preceded by a review of the medical history (especially with regard to previous immunisation and possible occurrence of undesirable events) and a clinical examination.

If any of the following events have occurred in temporal relation to receipt of DTPw or DTPa the decision to give subsequent doses of INFANRIX, containing the pertussis component, should be carefully considered.

There may be circumstances, such as a high incidence of pertussis, when the potential benefits outweigh possible risks, particularly since these events are not associated with permanent sequelae.

- Temperature of ≥40.5°C within 48 hours, not due to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours.
- Persistent, inconsolable crying lasting ≥ 3 hours, occurring within 48 hours.
- Convulsions with or without fever, occurring within 3 days.

Acute encephalopathy has been reported rarely (estimated rate 0-10.5 cases per million vaccinations) following whole-cell DTP vaccination; however a causal relationship has not been established. No such cases have been reported to date with acellular DTP vaccines.

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of anaphylactic reactions following the administration of the vaccine.

INFANRIX should be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration to these subjects.

HIV infection is not considered a contraindication for diphtheria, tetanus and pertussis (whole-cell or acellular) immunisation. However in patients with immunodeficiency or in patients receiving immunosuppressive therapy, an adequate immunologic response may not be achieved. No data currently exist on use of INFANRIX in these patients.

Interactions

INFANRIX was administered simultaneously with other paediatric vaccines (eg. Hib and oral polio) in some studies during the clinical trial programme, however immune responses to the other vaccines were not assessed.

Different injectable vaccines should always be administered at different injection sites. **INFANRIX must not be mixed with other vaccines.**

Use In Pregnancy

Adequate human data on use during pregnancy and adequate animal reproduction studies are not available.

Use In Lactation

Adequate human data on use during lactation and adequate animal reproduction studies are not available.

ADVERSE REACTIONS

Clinical Trial Experience

During controlled clinical studies, diary cards and a checklist were used to monitor signs and symptoms in all vaccinees following each administered dose of INFANRIX. The following table summarises pooled data from all studies for solicited symptoms reported within 48 hours of vaccination as a percentage of doses administered. Onset of the majority of local and general

symptoms occurred within 48 hours of vaccination. A causal relationship between these events and vaccination has not been established.

Solicited Symptoms	Frequency, %, (Number of doses, N*)		
	INFANRIX 3 dose primary immunisation course	INFANRIX after INFANRIX primary immunisation	INFANRIX after DTPw primary immunisation
Local reactions			
Pain	4.5 (11,406)	24.2 (1895)	24.1 (606)
Redness (> 2cm)	0.6 (11,406)	11.9 (1895)	3.5 (606)
Swelling (>2 cm)	0.4 (11,406)	11.0 (1895)	3.5 (606)
General Symptoms			
Fever, rectal (≥ 38°C)	9.0 (11,238)	26.6 (1895)	22.9 (606)
Fever, rectal (> 39.5°C)	0.1 (11,238)	0.8 (1895)	0.3 (606)
Eating/Drinking less than usual	7.4 (11,406)	11.7 (1895)	10.2 (498)
Unusual crying	4.2 (10,202)	6.7 (1843)	3.0 (328)
Constipation	1.1 (644)	-	-
Vomiting	4.0 (11,406)	3.1 (1895)	1.8 (606)
Diarrhoea	5.2 (12,202)	11.4 (1843)	6.0 (381)
Drowsiness	16.5 (1354)	10.3 (321)	8.6 (606)
Sleeping more than usual	9.3 (1275)	-	-
Sleeping less than usual	11.4 (2306)	10.8 (74)	7.7 (273)
Restlessness	9.0 (7896)	15.8 (1769)	3.8 (53)
Fussiness	-	-	26.7 (225)

** N = Number of doses for which diary card data on specified symptom were analysed.*

~~Redness and swelling of more than 10cm has been reported after INFANRIX booster dose. This resolved spontaneously. As with other vaccines such as DT and DTP, swelling of the entire thigh has occasionally been observed.~~

Comparative trials between INFANRIX and a DTPw vaccine have been conducted for primary immunisation or as a booster after INFANRIX or DTPw primary immunisation. The overall frequency of symptoms following the administration of INFANRIX was lower than that following DTPw vaccine, reaching statistical significance for most calculated symptom parameters. The following table summarises the results of individual comparative studies for solicited symptoms reported within 48 hours of vaccination as a percentage of doses administered. A causal relationship between these events and vaccination has not been established.

Solicited Symptoms	Frequency, %, following					
	Primary immunisation=		Booster immunisation*			
	Study APV-027		Study APV-027B		Study APV-044	
	INFANRIX (1275 doses)	DTPw‡ (455 doses)	INFANRIX after INFANRIX primary (269 doses)	DTPw‡ after DTPw‡ primary (92 doses)	INFANRIX after DTPw‡ primary (273 doses)	DTPw‡ after DTPw‡ primary (91 doses)
Local Symptoms						
Pain	2.5	19.1	15.6	55.4	15.8	59.3
Redness (> 2cm)	0.1	1.1	4.5	3.3	2.2	5.5
Swelling (> 2cm)	0	1.3	3.0	7.6	1.5	5.5
General Symptoms						
Fever, rectal ≥ 38°C	9.9	42.2	26.8	64.1	29.3	63.7
Fever, rectal > 39°C	0.2	1.3	0.4	4.3	0.7	4.4
Unusual crying	5.2	11.9	7.8	33.7	2.6	11.0
Vomiting	3.0	4.4	3.3	7.6	2.6	2.2
Diarrhoea	5.9	6.8	11.1	13.0	8.1	16.5
Eating/drinking less than usual	8.0	20.7	10.8	43.5	12.5	29.7
Drowsiness	-	-	10.4	31.5	-	-
Sleeping more than usual	9.3	16.7	-	-	10.3	14.3
Sleeping less than usual	9.3	13.6	-	-	13.2	16.5
Restlessness	-	-	12.3	32.6	-	-

= Primary immunisation doses administered at 3, 4, and 5 months of age.

‡ These studies used a DTP whole-cell vaccine not available in Australia

* Booster administered as fourth dose in the immunisation schedule.

Other events

Other unsolicited events reported in clinical trials for INFANRIX primary vaccination or booster doses after INFANRIX or DTPw primary courses are listed below. It should be noted however that causality has not necessarily been established for these events.

The events are listed within body systems and categorised by frequency according to the following definitions: **very common events reported at a frequency of greater or equal to 1/10 patients;** common events reported at a frequency of less than 1/10 but greater or equal to 1/100 patients; uncommon events reported at a frequency of less than 1/100 but greater or equal to 1/1,000 patients; rare events reported at a frequency of less than 1/1,000 patients **but greater or equal to 1/10,000 patients; very rare events reported at a frequency of less than 1/10,000 patients**.

INFANRIX primary immunisation ~~(total of 11406 documented doses)~~:

Dermatological: *Common:* dermatitis

Nervous System: *Common:* nervousness, somnolence

Respiratory: *Common:* coughing, rhinitis, bronchitis, other respiratory tract infection

Special Senses: *Common:* otitis media

INFANRIX booster following INFAINRIX primary immunisation ~~(total of 2363 documented doses)~~:

Body as a whole: *Common:* viral infection

Local reactions: *Very common: local swelling at the injection site ≤ 50 mm)
Common: injection site reaction; local swelling at the injection site (>50 mm)*
Uncommon: diffuse swelling of the injected limb, sometimes involving the adjacent joint***

Respiratory: *Common:* coughing, pharyngitis, bronchitis, other upper respiratory tract infection, rhinitis, respiratory disorder

Special Senses: *Common:* otitis media

***Children primed with acellular pertussis vaccines are more likely to experience swelling reactions after booster administration in comparison with children primed with whole cell vaccines. Local swelling at the injection site (>50 mm) and diffuse swelling may be more frequent (very common and common, respectively) when the booster dose is administered between 4 and 6 years. These reactions resolve over an average of 4 days.**

INFANRIX booster following DTPw primary immunisation (total of 606 documented doses):

Respiratory: *Common:* coughing, pharyngitis, bronchitis, upper respiratory tract infection

Special Senses: *Common:* otitis media

~~Large oedematous swelling leading to an increased circumference of the injected limb has been observed in clinical trial studies of booster doses of INFANRIX, with an incidence of approximately 1%. All these larger reactions with INFANRIX resolved without sequelae.~~

~~Post-marketing experience with INFANRIX is currently limited.~~
Post-marketing experience

Very rare swelling of the entire injected limb has been reported.

Extremely rare cases of collapse or shock-like state (hypotonic-hyporesponsiveness episode) and convulsions within 2 to 3 days of vaccination have been reported. All the subjects recovered totally and spontaneously without sequelae.

Very rare allergic reactions, including anaphylactoid reactions, have been reported.

DOSAGE AND ADMINISTRATION

All parenteral drug and vaccine products should be inspected visually for any particulate matter or discolouration prior to administration. Before use of INFANRIX, the vaccine should be well shaken to obtain a homogenous turbid suspension. Discard the vaccine if it appears otherwise.

Dosage

Each dose consists of a 0.5mL ready to use sterile suspension.

Administration

INFANRIX is administered by intramuscular injection. THE VACCINE SHOULD NEVER BE ADMINISTERED INTRAVENOUSLY.

INFANRIX should be injected intramuscularly in the lateral aspect of the thigh or the deltoid region of the arm. The recommended dose (0.5 mL) of vaccine must be administered.

Immunisation Schedule

The primary immunisation course consists of 3 doses at 2, 4 and 6 months of age, with a fourth dose at 18 months of age and a fifth dose at 4 to 5 years of age, before school entry.

INFANRIX can also be used as the fourth and/or fifth dose for children 18 months of age and 4 to 5 years of age, who have previously been immunised with three or four doses of diphtheria, tetanus and pertussis (whole-cell or acellular) vaccine.

STORAGE

INFANRIX should be stored at +2°C and +8°C. DO NOT FREEZE, discard if vaccine has been frozen. The expiry date of the vaccine is indicated on the label and packaging. The shelf life of INFANRIX is 36 months from the date of manufacture at a temperature of +2°C to +8°C.

PRESENTATIONS

INFANRIX is presented as a turbid white suspension in a glass vial or glass prefilled syringe. Upon storage a white deposit and clear supernatant can be observed.

The vials and prefilled syringes are made of neutral glass type I, which conforms to European Pharmacopoeia Requirements.

MANUFACTURER

GlaxoSmithKline Biologicals SA
rue de l'Institut 89
1330 Rixensart, Belgium.

DISTRIBUTED IN AUSTRALIA BY:

GlaxoSmithKline Australia Pty Ltd
1061 Mountain Highway
Boronia 3155 VIC

Date of TGA approval: ~~January 8, 1997~~ **TBA**
~~Date of last amendment: November 11, 2003~~

Issue 8

®INFANRIX is a registered trade mark of the GlaxoSmithKline group of companies

INFANRIX-HIB Product Information

INFANRIX®-Hib PRODUCT INFORMATION

Combined diphtheria-tetanus-acellular pertussis (DTPa)
and *Haemophilus influenzae* type b (Hib) vaccine

DESCRIPTION

INFANRIX-Hib is a non-infectious combination vaccine containing diphtheria toxoid, tetanus toxoid and three purified pertussis antigens: pertussis toxoid (PT), filamentous haemagglutinin (FHA), and pertactin (69 kiloDalton outer membrane protein). It also contains purified polyribosyl-ribitol-phosphate capsular polysaccharide (PRP) of *Haemophilus influenzae* type b (Hib) covalently bound to tetanus toxoid.

INFANRIX-Hib is supplied as a white lyophilised pellet of Hib vaccine for reconstitution with a sterile suspension of DTPa vaccine. Each 0.5mL dose contains 25Lf of adsorbed diphtheria toxoid, 10Lf of adsorbed tetanus toxoid, 25µg of PT, 25µg of FHA, 8µg of 69kDa OMP and purified capsular polysaccharide of Hib 10µg covalently bound to approximately 30µg of tetanus toxoid. The DTPa antigens are adsorbed onto aluminium salts. The reconstituted vaccine preparation also contains 2-phenoxyethanol, lactose, sodium chloride and water for injection.

INFANRIX-Hib is formulated using purified and detoxified diphtheria and tetanus toxins obtained from inactivated cultures of *Corynebacterium diphtheriae* and *Clostridium tetani.* The acellular pertussis vaccine components (PT, FHA, and pertactin) are extracted from phase I strain *Bordetella pertussis*, then purified and irreversibly detoxified. The DTPa components of INFANRIX-Hib are adsorbed onto aluminium salts, formulated in a saline suspension and preserved with 2-phenoxyethanol.

The Hib polysaccharide component of INFANRIX-Hib is extracted from cultures of *Haemophilus influenzae* type b strain 20,752 and coupled to tetanus toxoid. After purification, the Hib conjugate is lyophilised in the presence of a lactose stabiliser.

The manufacture of this product includes exposure to bovine derived materials. No evidence exists that any case of vCJD (considered to be the human form of bovine spongiform encephalopathy) has resulted from the administration of any vaccine product.

INFANRIX-Hib meets the World Health Organisation requirements for the manufacture of biological substances, of Hib conjugate vaccines, and of diphtheria, tetanus, pertussis and combined vaccines.

CLINICAL PHARMACOLOGY

The protective efficacy of INFANRIX-Hib has not been studied in field trials. INFANRIX-Hib induces the production of specific antibodies against diphtheria, tetanus, pertussis and *Haemophilus influenzae* type b (Hib) infection.

A booster dose of Infanrix-Hib was assessed in 93 subjects aged 15-27 months of age who had received a 3 dose primary course of DTPa and Hib vaccine given either as a mix, or as separate injections. One month following the booster dose, all subjects had anti PRP antibodies >0.15µg/ml, and 92 subjects (98.9%) had anti-PRP titres >1.0µg/ml. Booster response to pertussis antigens was defined as the appearance of titre for seronegative children and a two-fold increase in titre for seropositive children. Using these criteria, booster responses to PT, FHA and pertactin were demonstrated by 100 % of subjects.

Diphtheria and tetanus antibody titres of ≥ 0.1 IU/mL were elicited in 100% of vaccinees.

The protective efficacy of the pertussis antigens contained in Infanrix-Hib has been demonstrated following their administration with diphtheria and tetanus toxoids (DTPa vaccine, INFANRIX).

INDICATIONS

INFANRIX-Hib is indicated for use as a booster dose at 18 months in children who have had a primary course of immunisation with a conjugated Hib vaccine.

CONTRAINDICATIONS

INFANRIX-Hib should not be administered to subjects with known hypersensitivity to any component of the vaccine, or to subjects having shown signs of hypersensitivity after previous administration of diphtheria, tetanus, pertussis or Hib vaccines.

As for any vaccine, INFANRIX-Hib should not be administered to subjects suffering from acute severe febrile illness. However, the presence of minor infection does not contraindicate vaccination.

INFANRIX is contraindicated if the child has experienced an encephalopathy occurring within 7 days following previous vaccination with pertussis containing vaccine.

WARNINGS AND PRECAUTIONS

INFANRIX-Hib should never be administered intravenously.

As with any parenteral vaccine, a solution of 1 in 1,000 adrenaline and other appropriate medical treatment should always be readily available for immediate use, in cases of a rare anaphylaxis or anaphylactoid reaction following administration of the vaccine. The vaccinee should therefore remain under medical supervision for 30 minutes after immunisation.

It is good clinical practice that any vaccination be preceded by a review of medical history (especially with regard to previous vaccinations and possible adverse events) and a clinical examination.

If any of the following events occur in temporal relation to receipt of DTP-containing vaccines, the decision to give subsequent doses of vaccine containing the pertussis component should be carefully considered. There may be circumstances, such as a high incidence of pertussis, when the potential benefits outweigh possible risks; particularly since these events are not associated with permanent sequelae.

- Temperature of ≥40.5°C within 48 hours of vaccination, not due to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours of vaccination.
- Persistent, inconsolable crying lasting ≥ 3 hours occurring within 48 hours of vaccination.
- Convulsions with or without fever occurring within 3 days of vaccination.

Human immunodeficiency virus (HIV) infection is not a contraindication to vaccination. However an adequate antibody response may not be obtained in patients with an immunodeficiency disorder or in patients receiving immunosuppressive therapy (see Interactions).

INFANRIX-Hib should be administered subcutaneously in patients with thrombocytopenia or bleeding disorders (eg. haemophiliacs) since bleeding after intramuscular injection may occur in these patients (see DOSAGE AND ADMINISTRATION).

Acute encephalopathy has been reported rarely (estimated rate 0-10.5 cases per million vaccinations) following whole cell DTP vaccination; however a causal relationship has not been established. No such cases have been reported to date with acellular DTP vaccines.

Native populations (native Alaskans, native American Indians) with a high incidence of *Haemophilus influenzae* type b disease have shown a reduced antibody response to conjugated *Haemophilus influenzae* type b vaccines. The immunogenicity of INFANRIX-Hib has not been studied in the Australian aboriginal population and the possibility of a lower antibody response than that seen in clinical studies should be borne in mind. INFANRIX-Hib is not recommended for use in the Aboriginal community.

Urinary excretion of the capsular polysaccharide antigen has been reported following Hib vaccination. Therefore antigen detection within 1-2 weeks of vaccination may not be of diagnostic value in suspected Hib disease.

INFANRIX-Hib will not protect against diseases caused by other types of *Haemophilus influenzae*, or meningitis caused by other organisms.

Use *in* Pregnancy

As INFANRIX-Hib is not intended for use in adults, adequate human data on use during pregnancy and adequate animal reproduction studies are not available.

Use in Lactation

As INFANRIX-Hib is not intended for use in adults, adequate human data on use during lactation and adequate animal reproduction studies are not available.

Interactions

INFANRIX-HIB was administered simultaneously with other paediatric vaccines in studies during the clinical trial program. The immune responses to other vaccines have not been fully assessed. However, INFANRIX-Hib may be administered either simultaneously, or at any time before or after different live or inactivated vaccines. Different injectable vaccines administered concurrently should always be given in separate sites using separate syringes.

As with other vaccines, it may be expected patients receiving immunosuppressive therapy (eg high-dose steroids or cyclosporin) or patients with an immunodeficiency may not achieve an adequate immune response. (see WARNINGS AND PRECAUTIONS).

INFANRIX-Hib must not be mixed with other vaccines in the same syringe.

ADVERSE REACTIONS

During controlled clinical trials, diary cards were used to actively monitor signs and symptoms following INFANRIX-Hib vaccination.

The following table summarises the incidence of solicited symptoms reported within 48 hours of vaccination, as a percentage of doses administered. Onset of the majority of symptoms occurred within 48 hours of vaccination. A causal relationship has not been established.

Solicited Symptoms	Frequency , %		
	Vaccine given as a mix (n=138)	Vaccines given separately (n=40)	
	DTPa-Hib	DTPa	Hib
Local Reaction			
Pain	14.5	10.0	10.0
Redness (>2cm)	11.6	12.5	10.0
Swelling (>2cm)	4.3	5.0	5.0
General Symptoms			
Fever, rectal (≥ 38°C)	24.6	30.0	
Loss of appetite	12.3	17.5	
Restlessness	15.2	22.5	
Unusual crying	8.7	10.0	
Vomiting	1.4	5.0	
Diarrhoea	10.1	10.0	

Other events

Unsolicited events reported in clinical trials **or reported during post-marketing surveillance** for booster doses of INFANRIX-Hib are listed below. It should be noted however that causality has not necessarily been established for these events.

The events are listed within body systems and categorised by frequency according to the following definitions: **very common events reported at a frequency of greater or equal to 1/10 patients;** common events reported at a frequency of less than 1/10 but greater or equal to 1/100 patients; uncommon events reported at a frequency of less than 1/100 but greater or equal to 1/1,000 patients; rare events reported at a frequency of less than 1/1,000 patients **but greater or equal to 1/10,000 patients; very rare events reported at a frequency of less than 1/10,000 patients**.

Application site:

Very common: **local swelling at the injection site ≤ 50mm.**

Common: **local swelling at the injection site >50mm.**

Uncommon: **diffuse swelling of the injected limb, sometimes involving the adjacent joint.**

Very rare: **swelling of the entire injected limb has been observed during post-marketing surveillance.**

Children primed with acellular pertussis vaccines are more likely to experience swelling reactions after booster administration in comparison with children primed with whole cell vaccines. These reactions resolve over an average of 4 days.

Body as a whole:

Common: injury.

Uncommon: **fever (≥ 39.5°C rectal).**

Very rare: **allergic reactions including anaphylactoid reactions.**

Gastrointestinal:

Common: enteritis, gastroenteritis.

Uncommon: constipation, stomatitis, tooth disorder.

CNS:

Uncommon: convulsions, **febrile convulsions.**

Respiratory system:

Very common: respiratory disorder.

Common: bronchitis, pharyngitis, rhinitis.

Uncommon: stridor.

White cell and RSE disorders:

Uncommon: lymphadenopathy.

Resistance mechanisms:

Common: Upper respiratory tract infection, infection, viral infection, otitis media.

Vision disorders:

Common: conjunctivitis.

Hearing and vestibular disorders:

Common: ear disorders.

Psychiatric:

***Very common:* somnolence.**

Uncommon: agitation.

In clinical studies, fewer adverse events were observed with DTP vaccines containing an acellular pertussis component, such as INFANRIX-Hib, as compared to whole-cell DTP vaccines.

~~Large oedematous swelling leading to an increased circumference of the injected limb has been observed in clinical trial studies of booster doses of Infanrix, with an incidence of approximately 1%, but has not been reported to date following booster administration of Infanrix Hib. All these larger reactions with Infanrix resolved without sequelae.~~

Extremely rare cases of collapse or shock-like state (hypotonic-hyporesponsiveness) and convulsions within 2 to 3 days of vaccination have been reported. All the subjects recovered totally and spontaneously without sequelae.

DOSAGE AND ADMINISTRATION

INFANRIX-Hib vaccine is supplied as a white lyophilised pellet of Hib vaccine for reconstitution with a sterile suspension of DTPa vaccine. The DTPa vaccine must be shaken well before use in order to obtain an homogenous white turbid suspension, since upon storage the vaccine settles down as a fine white deposit with a clear colourless supernatant. INFANRIX-Hib is reconstituted by adding the entire contents of the DTPa vaccine container to the vial containing the Hib vaccine pellet. The reconstituted solution must be shaken well before use, and must not be injected prior to complete dissolution of the Hib pellet. After shaking the vaccine is a slightly opaque, white suspension. Discard if the contents of the vial appear otherwise. All parenteral drug and vaccine products should be inspected visually prior to administration for foreign particulate matter and/or discolouration. INFANRIX-Hib should be promptly administered after reconstitution.

The recommended dose is 0.5mL.

INFANRIX-Hib vaccine must be administered by deep intramuscular injection. The injection should be given in the deltoid region. The vaccine should be administered subcutaneously in patients with thrombocytopenia or bleeding tendencies (eg. haemophiliacs). (see WARNINGS AND PRECAUTIONS). It is recommended that subsequent INFANRIX-Hib vaccine doses be administered at alternated injection sites.

INFANRIX-Hib MUST NOT BE GIVEN INTRAVENOUSLY.

STORAGE

INFANRIX-Hib (DTPa vaccine suspension and lyophilised Hib vaccine pellet) must be stored between +2°C to +8°C, and protected from light.

DO NOT FREEZE the DTPa vaccine suspension, as freezing destroys the potency of the product. Discard the vaccine if it has been frozen. Lyophilised Hib vaccine is not affected by freezing.

The shelf-life of INFANRIX-Hib is three years from the date of manufacture when stored at temperatures between +2°C to +8°C.

The expiry date of the vaccine is marked on the label and packaging.

PRESENTATIONS

The DTPa vaccine suspension is supplied in a glass vial or prefilled syringe. The lyophilised Hib vaccine is presented as a white pellet in a glass vial.

INFANRIX-Hib pack sizes are: monodose packs of 1.

The vials and prefilled syringes are made of neutral glass type 1. which conforms to European Pharmacopoeia requirements.

MANUFACTURER

GlaxoSmithKline Biologicals SA
rue de l'Institut 89
1330 Rixensart, Belgium.

DISTRIBUTED IN AUSTRALIA BY

GlaxoSmithKline Australia Pty Ltd
1061 Mountain Highway
Boronia 3155 VIC

Date of TGA Approval: TBA

Issue 4

®INFANRIX is a registered trade mark of the GlaxoSmithKline group of companies

1.3.2. Australian Consumer Information

Document 1

MANILLA
WHITE DIVIDERS
5 TAB A4

marbig

Ref No:37320
Made in China
www.accobrands.com.au

INFANRIX HEXA Consumer Medicine Information

INFANRIX® hexa

Combined Diphtheria-Tetanus-acellular Pertussis (DTPa), Hepatitis B, Inactivated Poliovirus and Haemophilus influenzae type b Vaccine

CONSUMER MEDICINE INFORMATION LEAFLET

WHAT IS IN THIS LEAFLET

This leaflet answers some of the common questions about INFANRIX hexa vaccine. It does not contain all the available information. It does not take the place of talking to your doctor, nurse or pharmacist.

All medicines and vaccines have risks and benefits. Your doctor has weighed the possible risks of your child having INFANRIX hexa against the expected benefits.

If you have any concerns about your child receiving INFANRIX hexa talk to your doctor, nurse or pharmacist.

Keep this leaflet with this vaccine. You may need to read it again.

WHAT INFANRIX hexa IS USED FOR

INFANRIX hexa is a vaccine used to prevent six diseases: diphtheria, tetanus, pertussis (whooping cough), hepatitis B, poliomyelitis (polio) and *Haemophilus influenzae* type b (Hib). The vaccine works by causing the body to produce its own protection (antibodies) against these diseases.

Diphtheria, tetanus, pertussis and Hib are all serious life-threatening diseases caused by bacterial infection. Hepatitis B and poliomyelitis are infectious diseases caused by viral infection.

Diphtheria
Diphtheria mainly affects the airways and sometimes the skin. Generally the airways become inflamed (swollen) causing severe breathing difficulties and sometimes suffocation. The bacteria also release a toxin (poison), which can cause nerve damage, heart problems, and death. The risk of serious complications and death is greater in the very young and elderly.

Tetanus (Lockjaw)
Tetanus bacteria enter the body through wounded skin. Wounds that are especially prone to infection are burns, fractures, deep wounds or wounds contaminated with soil, dust, horse manure or wood splinters. The bacteria release a toxin (poison), which can cause muscle stiffness, painful muscle spasms, fits and death. The spasms can be strong enough to cause bone fractures of the spine. The death rate is 10% of cases.

Pertussis (Whooping cough)
Pertussis is a highly infectious illness. The disease affects the breathing tract causing severe spells of coughing that may interfere with normal breathing. The coughing is often accompanied by a 'whooping' sound. The cough may last for 1-2 months or longer. Pertussis can also cause inner ear infections, long-lasting bronchitis, pneumonia, fits, brain damage and death. The risk of severe complications and death is greatest in infants under 6 months of age. The death rate is 0.5% for infants under 6 months of age.

Hepatitis B
Hepatitis B is caused by the hepatitis B virus. It causes the liver to be become swollen (inflamed). The virus is found in body fluids such as blood, semen, vaginal secretions, or saliva of infected people. The virus can enter the bloodstream through:

- an infected mother passing the virus onto her baby during or shortly after birth
- sores, cuts or tiny wounds coming into contact with infected fluids (eg from a human bite, sharing razors or toothbrushes, or working with human blood or body fluids)
- injection (eg needlestick injury, or sharing needles for IV drug use)
- sexual intercourse

Some people infected with hepatitis B may not look or feel sick. But others will get symptoms, which may not be seen for 6 weeks to 6 months after infection. Sometimes people will only have mild flu-like symptoms, but other people can become very ill. They may be extremely tired, and have dark urine, pale faeces, yellowish skin and/or eyes (jaundice), and other symptoms possibly requiring hospitalisation.

Most adults fully recover from the disease. However, some people, particularly children, who may not have had symptoms, can remain infected. They are called hepatitis B virus carriers. Hepatitis B carriers can infect others throughout their lives.

Babies infected with hepatitis B at birth almost always become carriers. Often they do not show symptoms, and seem healthy for many years. However, after 30, 40 or 50 years they can become sick and develop symptoms. For all chronic hepatitis B carriers there is a risk of serious liver disease, such as cirrhosis (liver scarring) and liver cancer.

There is no specific treatment for hepatitis B.

Poliomyelitis (Polio)
Polio is a viral infection that can have variable effects. Often it causes only a mild illness but in some people it causes permanent injury or death.

In its severest form, polio infection causes paralysis of the muscles, including those needed for breathing and walking. Polio infection can leave a person unable to breathe without the help of an iron lung machine, unable to walk without leg braces, or confined to a wheel chair. The limbs affected by the disease may be painfully deformed.

***Haemophilus influenzae* type b (Hib)**
Hib most frequently causes brain inflammation (swelling), which is generally seen in infants under 18 months of age. The death rate is 5-10% of infants in this age group. In 15-30% of surviving infants there will be some type of serious complication such as: mental retardation, cerebral palsy, deafness, epilepsy or partial blindness. Hib also causes inflammation of the throat, which is mostly seen in children over 18 months of age. It occasionally causes death by suffocation. Less commonly, the bacteria can also infect the blood, heart, lungs, bones, joints, and tissues of the eyes and mouth.

Vaccination is the best way to protect against these diseases. INFANRIX hexa vaccine cannot give your child diphtheria, tetanus, pertussis, hepatitis B or polio infection. The vaccine will not protect against diseases caused by other types of bacteria, viruses or organisms. If a person is already infected with the hepatitis B virus at the time of vaccination, INFANRIX hexa may not prevent the disease in these people.

BEFORE VACCINATION

INFANRIX hexa SHOULD NOT BE GIVEN IF :

- your child has had an allergic reaction to INFANRIX hexa, or any ingredient contained in this vaccine. The ingredients in INFANRIX hexa are listed at the end of this leaflet. Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.

  If your child had INFANRIX hexa before and became unwell, tell your doctor, nurse or pharmacist before the next dose is given.

- your child experienced a disease of the brain within 7 days after previous vaccination with a pertussis containing vaccine.
- your child has had an allergic reaction to any other diphtheria, tetanus, hepatitis B, inactivated polio or *Haemophilus influenzae* type b vaccine (such as ENGERIX-B®, H-B-Vax II™, INFANRIX®, Triple Antigen™, Tripacel™ or IPOL™ vaccine, HIBERIX®).
- your child has a severe infection with a high temperature. A minor infection such as a cold should not be a problem, but talk to your doctor or nurse about this before vaccination.
- the expiry date printed on the pack has passed.
- the packaging is torn or shows signs of tampering.

If you are not sure whether your child should have INFANRIX hexa vaccine, talk to your doctor or nurse. Do not give this vaccine to anyone

else; your doctor has prescribed it specifically for your child.

BEFORE INFANRIX hexa IS GIVEN TELL YOUR DOCTOR OR NURSE IF:

- your child has any medical problems such as:
  - brain disease or central nervous system (CNS) disease (ie. epilepsy etc.)
  - a bleeding problem or bruises easily
  - lowered immunity due to medical treatment or a medical condition
  - a tendency to febrile convulsions (seizures/fits due to a fever or high body temperature)
  - a family history of seizures/fits
  - a family history of Sudden Infant Death Syndrome (SIDS)
  - allergy to the antibiotics: neomycin and polymyxin.
- after having INFANRIX hexa or another pertussis-containing vaccine (such as INFANRIX® or Tripacel) your child had any problems, especially:
  - a high temperature (over 40.5°C) within 2 days of vaccination
  - a collapse or shock-like state within 2 days of vaccination
  - crying lasting 3 hours or more within 2 days of vaccination
  - convulsions (seizures/fits) with or without a fever within 3 days of vaccination
- your child has allergies to any other medicines or substances, such as dyes, foods or preservatives
- your child has received another vaccine recently, or is having any prescription or OTC (over-the-counter) medicines. In particular, mention if your child is being given medicines which suppress the immune system, such as high-dose steroids

Some vaccines may be affected by other vaccines or medicines. Your doctor, nurse or pharmacist will be able to tell you what to do if INFANRIX hexa is to be given with another vaccine or medicine.

HOW INFANRIX hexa IS GIVEN

The doctor or nurse will give INFANRIX hexa as an injection. **If you have any concerns about how this vaccine is to be given, talk to your doctor, nurse or pharmacist.**

HOW MUCH IS GIVEN

The dose of INFANRIX hexa is 0.5mL.

HOW IT IS GIVEN

INFANRIX hexa will be injected into the upper leg muscle in infants under 12 months of age. In children over 12 months of age, INFANRIX hexa will usually be injected into the upper arm muscle.

The vaccine should never be given intravenously.

WHEN IT IS GIVEN

INFANRIX hexa is usually given as a total of three doses as follows:

First dose: 2 months of age
Second dose: 4 months of age
Third dose: 6 months of age

Each dose is given on a separate visit. INFANRIX hexa should not be given at birth.

It is important to return at the recommended times for follow-up doses.
INFANRIX hexa can be given as a booster dose when the child is 18 months old when boosting with hepatitis B and/or poliovirus and/or *Haemophilus influenzae* type b, as well as diphtheria, tetanus and pertussis, is required.

A booster dose of tetanus and diphtheria vaccine will be required at 15–19 years of age and at 50 years of age.

You should discuss with your doctor what is needed for your child.

IF A DOSE IS MISSED

If your child misses a scheduled dose, talk to your doctor or nurse and arrange another visit as soon as possible.

WHILE USING INFANRIX hexa

Keep your child's follow-up visits with the doctor or clinic. It is important the follow-up doses of INFANRIX hexa are given at the correct times. This will ensure the best effect of the vaccine in protecting your child against diphtheria, tetanus, pertussis, hepatitis B, poliovirus infection and *Haemophilus influenzae* type b.

SIDE EFFECTS

Tell your doctor or nurse as soon as possible if your child does not feel or look well during or after having had a dose of INFANRIX hexa vaccine.

INFANRIX hexa helps protect most children from diphtheria, tetanus, pertussis, hepatitis B, poliovirus infection and *Haemophilus influenzae* type b, but it may have unwanted side effects in a few children. All medicines and vaccines can have side effects. Sometimes they are serious; most of the time they are not. Some side effects may need medical treatment. The chance of your child having a serious side effect is very much less than the chance of your child having a permanent injury from the natural infections.

Ask your doctor, nurse or pharmacist to answer any questions you may have.
Most unwanted effects with INFANRIX hexa are mild and usually clear up within a few days. These effects, as with other vaccines, generally occur around the injection site. Side effects are more likely to occur with booster dosing.

MILD EFFECTS

- **Tell your doctor if your child has any of the following that are troublesome or ongoing:**
  - pain, redness, swelling, a hard lump, bruising or itching around the injection site
  - fever between 38°C and 39.5°C
  - unusual crying (for more than 1 hour), vomiting, diarrhoea, runny nose or loss of appetite
  - sleepiness, nervousness, irritability restlessness, fussiness or difficulty sleeping
  - skin rash, bruising, or purple or red-brown spots visible through the skin (purpura)

MORE SERIOUS EFFECTS

- **Tell your doctor immediately if you notice any of the following:**
  - fever greater than 39.5°C
  - crying for 3 hours or more
  - collapse, or periods of unconsciousness or lack of awareness
  - seizures (convulsions) or fits
- **Contact your doctor immediately or take your child to the casualty department of your nearest hospital if any of the following happens:**
  - swelling of limbs, face, eyes, inside of nose, mouth or throat
  - shortness of breath, breathing or swallowing difficulties
  - hives, itching (especially of the hands or feet), reddening of skin (especially around the ears), or severe skin reactions
  - unusual tiredness or weakness that is sudden and severe

These are signs of an allergic reaction. As with all vaccines given by injection there is a very small risk of such reactions. Allergy to INFANRIX hexa vaccine is rare. Any such severe reactions will usually occur within the first few hours of vaccination.

- **Other events reported after INFANRIX vaccination, but not be necessarily related to the vaccine include:**
  - respiratory infections or bronchitis

Other side effects not listed above, can also occur during or soon after a dose of INFANRIX hexa. **Check with your doctor or nurse if your child has any other effects.**

Do not be alarmed by this list of possible side effects. Your child may not experience any of them.

STORAGE

INFANRIX hexa vaccine is usually stored at the doctor's clinic or surgery, or at the pharmacy. But if you need to store INFANRIX hexa always:

- Keep INFANRIX hexa in the refrigerator stored between +2°C and +8°C. **THE PACK SHOULD NEVER BE FROZEN. FREEZING DESTROYS THE VACCINE.**
- Keep the vaccine out of the reach of children.
- INFANRIX hexa should not be used 8 hours after opening.
- Keep INFANRIX hexa in the original pack until it is time for it to be given.

Ask your pharmacist what to do with any left over INFANRIX hexa vaccine that has expired or has not been used.

PRODUCT DESCRIPTION

WHAT IT LOOKS LIKE

INFANRIX hexa comes in two parts. The first part is a white, milky liquid (0.5mL) in a pre-filled syringe that consists of the combined diphtheria, tetanus, pertussis, hepatitis B and inactivated poliovirus vaccine. The second part is the Hib vaccine and is a white pellet in a separate glass vial. These parts are mixed together before use.

When both parts are mixed the vaccine looks like a white, cloudy/milky liquid.

INGREDIENTS

The active ingredients of INFANRIX hexa are non-infectious substances from tetanus, diphtheria bacteria, purified proteins of pertussis bacteria, the surface protein of the hepatitis B virus (HBsAg, derived from genetically engineered yeast cells) and inactivated poliovirus. **The vaccine cannot cause these diseases.** Each 0.5mL dose contains:

- ≥30 IU (25 LfU) of diphtheria toxoid
- ≥40 IU (10 Lf U) of tetanus toxoid
- 25µg of pertussis toxoid, 25µg of filamentous haemagglutinin and 8µg of pertactin
- 10µg of recombinant HBsAg protein.
- 40 D-antigen units of poliovirus Type 1, 8 D-antigen units of poliovirus Type 2 and 32 D-antigen units of poliovirus Type 3
- 10µg of purified capsular polysaccharide of Hib covalently bound to approximately 20-40µg of tetanus toxoid.

The inactive ingredients in the vaccine are: aluminium hydroxide, aluminium phosphate, 2-phenoxyethanol, lactose, Medium 199, neomycin (traces), polymyxin (traces), polysorbate 80, polysorbate 20, sodium chloride (salt) and water.

The manufacture of this product includes exposure to bovine derived materials. No evidence exists that any case of vCJD (considered to be the human form of bovine spongiform encephalopathy) has resulted from the administration of any vaccine product.

FURTHER INFORMATION

INFANRIX hexa is only available if prescribed by a doctor.

INFANRIX hexa comes in two parts; a pre-filled syringe containing the combined DTPa, hepatitis B and polio vaccine and a separate glass vial containing the Hib vaccine (AUST R 79078).

MANUFACTURER

GlaxoSmithKline Biologicals
Rue de l'Institut
89
1330
Rixensart,
Belgium.

DISTRIBUTED IN AUSTRALIA BY:
GlaxoSmithKline Australia Pty. Ltd.
1061 Mountain Highway
Boronia VIC
3155

Date of Preparation:
13 November 2003

INFANRIX PENTA Consumer Medicine Information

INFANRIX® PENTA

Combined Diphtheria-Tetanus-acellular Pertussis (DTPa), Hepatitis B and Inactivated Poliovirus Vaccine

CONSUMER MEDICINE INFORMATION LEAFLET

WHAT IS IN THIS LEAFLET

This leaflet answers some of the common questions about INFANRIX PENTA vaccine. It does not contain all the available information. It does not take the place of talking to your doctor, nurse or pharmacist.

All medicines and vaccines have risks and benefits. Your doctor has weighed the possible risks of your child having INFANRIX PENTA against the expected benefits.

If you have any concerns about your child receiving INFANRIX PENTA talk to your doctor, nurse or pharmacist.

Keep this leaflet with this vaccine. You may need to read it again

WHAT INFANRIX PENTA IS USED FOR

INFANRIX PENTA is a vaccine used to prevent five diseases, diphtheria, tetanus, pertussis (whooping cough), hepatitis B and poliomyelitis (polio). The vaccine works by causing the body to produce its own protection (antibodies) against these diseases.

Diphtheria, tetanus, and pertussis are all serious life-threatening diseases caused by bacterial infection. Hepatitis B and poliomyelitis are infectious diseases caused by viral infection.

Diphtheria
Diphtheria mainly affects the airways and sometimes the skin. Generally the airways become inflamed (swollen) causing severe breathing difficulties and sometimes suffocation. The bacteria also release a toxin (poison), which can cause nerve damage, heart problems, and death. The risk of serious complications and death is greater in the very young and elderly.

Tetanus (Lockjaw)
Tetanus bacteria enter the body through wounded skin. Wounds that are especially prone to infection are burns, fractures, deep wounds or wounds contaminated with soil, dust, horse manure or wood splinters. The bacteria release a toxin (poison), which can cause muscle stiffness, painful muscle spasms, fits and death. The spasms can be strong enough to cause bone fractures of the spine. The death rate is 30-40% of cases.

Pertussis (Whooping cough)
Pertussis is a highly infectious illness. The disease affects the breathing tract causing severe spells of coughing that may interfere with normal breathing. The coughing is often accompanied by a 'whooping' sound. The cough may last for 1-2 months or longer. Pertussis can also cause inner ear infections, long-lasting bronchitis, pneumonia, fits, brain damage and death. The risk of severe complications and death is greatest in infants under 6 months of age. The death rate is 0.5% for infants under 6 months of age.

Hepatitis B
Hepatitis B is caused by the hepatitis B virus. It causes the liver to become swollen (inflamed). The virus is found in body fluids such as blood, semen, vaginal secretions, or saliva of infected people. The virus can enter the bloodstream through:

- an infected mother passing the virus onto her baby during or shortly after birth
- sores, cuts or tiny wounds coming into contact with infected fluids (eg from a human bite, sharing razors or toothbrushes, or working with human blood or body fluids)
- injection (eg needlestick injury, or sharing needles for IV drug use)
- sexual intercourse

Some people infected with hepatitis B may not look or feel sick. But others will get symptoms, which may not be seen for 6 weeks to 6 months

after infection. Sometimes people will only have mild flu-like symptoms, but other people can become very ill. They may be extremely tired, and have dark urine, pale faeces, yellowish skin and/or eyes (jaundice). and other symptoms possibly requiring hospitalisation.

Most adults fully recover from the disease. But some people, particularly children who may not have had symptoms, can remain infected. They are called hepatitis B virus carriers. Hepatitis B carriers can infect others throughout their lives.

Babies infected with hepatitis B at birth almost always become carriers. Often they do not show symptoms, and seem healthy for many years. However, after 30, 40 or 50 years they can become sick and develop symptoms. For all chronic hepatitis B carriers there is a risk of serious liver disease, such as cirrhosis (liver scarring) and liver cancer.

There is no specific treatment for hepatitis B.

Poliomyelitis (Polio)
Polio is a viral infection that can have variable effects. Often it causes only a mild illness but in some people it causes permanent injury or death.

In its severest form, polio infection causes paralysis of the muscles, including those needed for breathing and walking. Polio infection can leave a person unable to breathe without the help of an iron lung machine, unable to walk without leg braces, or confined to a wheel chair.

The limbs affected by the disease may be painfully deformed.

Vaccination is the best way to protect against these diseases. INFANRIX PENTA vaccine cannot give your child diphtheria, tetanus, pertussis, hepatitis B or polio infection. The vaccine will not protect against diseases caused by other types of bacteria, viruses or organisms. If a person is already infected with the hepatitis B virus at the time of vaccination, INFANRIX PENTA may not prevent the disease in these people.

BEFORE VACCINATION

INFANRIX PENTA SHOULD NOT BE GIVEN IF:

- your child has had an allergic reaction to INFANRIX PENTA, or any ingredient contained in this vaccine. The ingredients in INFANRIX PENTA are listed at the end of this leaflet. Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.

  If your child had INFANRIX PENTA before and became unwell, tell your doctor, nurse or pharmacist before the next dose is given.

- your child experienced a disease of the brain within 7 days after previous vaccination with a pertussis containing vaccine.
- your child has had an allergic reaction to any other diphtheria, tetanus, hepatitis B or inactivated polio containing vaccine (such as Engerix®-B, H-B-Vax II™, Infanrix®, Triple Antigen™, Tripacel™ or IPOL™ vaccine).
- your child has a severe infection with a high temperature. A minor infection such as a cold should not be a problem, but talk to your doctor or nurse about this before vaccination.
- the expiry date printed on the pack has passed.
- the packaging is torn or shows signs of tampering.

If you are not sure whether your child should have INFANRIX PENTA vaccine, talk to your doctor or nurse. Do not give this vaccine to anyone else; your doctor has prescribed it specifically for your child.

BEFORE INFANRIX PENTA IS GIVEN TELL YOUR DOCTOR OR NURSE IF:

- your child has any medical problems such as:
  - brain disease or central nervous system (CNS) disease (ie. epilepsy etc.)
  - a bleeding problem or bruises easily
  - lowered immunity due to medical treatment or a medical condition
  - a tendency to febrile convulsions (seizures/fits due to a fever or high body temperature)
  - a family history of Sudden Infant Death Syndrome (SIDS)
  - allergy to the antibiotics: neomycin and polymyxin.
- after having INFANRIX PENTA or another pertussis-containing vaccine (such as Infanrix® or Triple Antigen) your child had any problems, especially:

- a high temperature (over 40.5°C) within 2 days of vaccination
- a collapse or shock-like state within 2 days of vaccination
- crying lasting 3 hours or more within 2 days of vaccination
- convulsions (seizures/fits) with or without a fever within 3 days of vaccination

- your child has allergies to any other medicines or substances, such as dyes, foods or preservatives

- your child has received another vaccine recently, or is having any prescription or OTC (over-the-counter) medicines. In particular, mention if your child is being given medicines which suppress the immune system, such as high-dose steroids

Some vaccines may be affected by other vaccines or medicines. Your doctor, nurse or pharmacist will be able to tell you what to do if INFANRIX PENTA is to be given with another vaccine or medicine.

HOW INFANRIX PENTA IS GIVEN

The doctor or nurse will give INFANRIX PENTA as an injection. **If you have any concerns about how this vaccine is to be given, talk to your doctor, nurse or pharmacist.**

HOW MUCH IS GIVEN

The dose of INFANRIX PENTA is 0.5mL.

HOW IT IS GIVEN

INFANRIX PENTA will be injected into the upper leg muscle in infants under 12 months of age. In children over 12 months of age the injection may be given in the upper arm muscle instead.

The vaccine should never be given intravenously.

WHEN IT IS GIVEN

INFANRIX PENTA is usually given as a total of three doses as follows:

- First dose: 2 months of age
- Second dose: 4 months of age
- Third dose: 6 months of age

Each dose is given on a separate visit. INFANRIX PENTA should not be given at birth.

It is important to return at the recommended times for follow up doses.

A booster dose of INFANRIX PENTA may be given when the child is 18 months old if boosting with hepatitis B and/or poliovirus, as well as diphtheria, tetanus and pertussis, is required.

You should discuss with your doctor what is needed for your child.

IF A DOSE IS MISSED

If your child misses a scheduled dose, talk to your doctor or nurse and arrange another visit as soon as possible.

WHILE USING INFANRIX PENTA

THINGS YOU MUST DO:

Keep your child's follow up visits with the doctor or clinic. It is important the follow-up doses of INFANRIX PENTA are given at the correct times. This will ensure the best effect of the vaccine in protecting your child against diphtheria, tetanus, pertussis, hepatitis B and poliovirus infection.

SIDE EFFECTS

Tell your doctor or nurse as soon as possible if your child does not feel or look well during or after having had a dose of INFANRIX PENTA vaccine.

INFANRIX PENTA helps protect most children from diphtheria, tetanus, pertussis, hepatitis B and poliovirus infection, but it may have unwanted side effects in a few children. All medicines and vaccines can have side effects. Sometimes they are serious; most of the time they are not. Some side effects may need medical treatment. The chance of your child having a serious side effect is very much less than the chance of your child having a permanent injury from the natural infections.

Ask your doctor, nurse or pharmacist to answer any questions you may have.

Most unwanted effects with INFANRIX PENTA are mild and usually clear up within a few days. These effects, as with other vaccines, generally occur around the injection site. Side effects are more likely to occur with booster dosing.

MILD EFFECTS

- **Tell your doctor if your child has any of the following that are troublesome or ongoing:**
  - pain, redness, swelling, a hard lump, bruising or itching around the injection site
  - fever between 38°C and 39.5°C
  - unusual crying (for more than 1 hour), vomiting, diarrhoea, runny nose or loss of appetite
  - sleepiness, tiredness, nervousness, restlessness, fussiness or difficulty sleeping
  - skin rash, bruising, or purple or red-brown spots visible through the skin (purpura)

MORE SERIOUS EFFECTS

- **Tell your doctor immediately if you notice any of the following:**
  - fever greater than 39.5°C
  - crying for 3 hours or more
  - collapse, or periods of unconsciousness or lack of awareness
  - seizures (convulsions) or fits

- **Contact your doctor immediately or take your child to the casualty department of your nearest hospital if any of the following happens:**
  - swelling of limbs, face, eyes, inside of nose, mouth or throat
  - shortness of breath, breathing or swallowing difficulties
  - hives, itching (especially of the hands or feet), reddening of skin (especially around the ears), or severe skin reactions
  - unusual tiredness or weakness that is sudden and severe

These are signs of an allergic reaction. As with all vaccines given by injection there is a very small risk of such reactions. Allergy to INFANRIX PENTA *vaccine is rare. Any such severe reactions will usually occur within the first few hours of vaccination.*

- **Other events reported after INFANRIX vaccination, but not necessarily related to the vaccine include:**
  - respiratory infections, bronchitis or viral infection
  - infection of the middle ear that may cause earache and temporary hearing loss

Other side effects not listed above, can also occur during or soon after a dose of INFANRIX PENTA. **Check with your doctor or nurse if your child has any other effects.**

Do not be alarmed by this list of possible side effects. Your child may not experience any of them.

STORAGE

INFANRIX PENTA vaccine is usually stored at the doctor's clinic or surgery, or at the pharmacy. But if you need to store INFANRIX PENTA always:

- Keep INFANRIX PENTA in the refrigerator stored between +2°C and +8°C. **THE PACK SHOULD NEVER BE FROZEN. FREEZING DESTROYS THE VACCINE.**
- Keep the vaccine out of the reach of children.
- INFANRIX PENTA should not be used 8 hours after opening.
- Keep INFANRIX PENTA in the original pack until it is time for it to be given.

Ask your pharmacist what to do with any left over INFANRIX PENTA vaccine that has expired or has not been used.

PRODUCT DESCRIPTION

WHAT IT LOOKS LIKE

INFANRIX PENTA comes in a prefilled syringe or a vial. It is a white, slightly milky liquid.

INGREDIENTS

The active ingredients of INFANRIX PENTA are non-infectious substances from tetanus, diphtheria bacteria, purified proteins of pertussis bacteria, the surface protein of the hepatitis B virus (HBsAg, derived from genetically engineered yeast cells) and inactivated poliovirus. **The vaccine cannot cause these diseases.** Each 0.5mL dose contains:

- 30 IU (25 Lf U)of diphtheria toxoid
- 40 IU (10 Lf U) of tetanus toxoid

- 25mcg of pertussis toxoid, 25mcg of filamentous haemagglutinin and 8mcg of pertactin
- 10mcg of recombinant HBsAg protein.
- 40 D-antigen units of poliovirus Type 1, 8 D-antigen units of poliovirus Type 2 and 32 D-antigen units of poliovirus Type 3

The inactive ingredients in the vaccine are: aluminium hydroxide, aluminium phosphate, 2-phenoxyethanol, neomycin (traces), polymyxin (traces), polysorbate 20, polysorbate 80, Medium 199, sodium chloride (salt), formaldehyde, glycine, potassium chloride, sodium phosphate dibasic dihydrate, potassium phosphate monobasic and water.

The manufacture of this product includes exposure to bovine derived materials. No evidence exists that any case of vCJD (considered to be the human form of bovine spongiform encephalopathy) has resulted from the administration of any vaccine product.

FURTHER INFORMATION

INFANRIX PENTA is only available if prescribed by a doctor.

INFANRIX PENTA comes in a prefilled syringe (AUST R 79079) or in a vial* (AUST R 79991).

MANUFACTURER

GlaxoSmithKline Biologicals
Rue de l'Institut 89,
1330 Rixensart, Belgium.

DISTRIBUTED IN AUSTRALIA BY
GlaxoSmithKline Australia Pty. Ltd.
1061 Mountain Highway
Boronia VIC 3155

Date of Preparation:
11 November 2003

* The vial presentation is not currently marketed in Australia.

INFANRIX-IPV Consumer Medicine Information

INFANRIX®-IPV

Combined Diphtheria-Tetanus-acellular Pertussis (DTPa) and Inactivated Poliovirus Vaccine

CONSUMER MEDICINE INFORMATION LEAFLET

WHAT IS IN THIS LEAFLET

This leaflet answers some of the common questions about INFANRIX®-IPV vaccine. It does not contain all the available information. It does not take the place of talking to your doctor, nurse or pharmacist.

All medicines and vaccines have risks and benefits. Your doctor has weighed the possible risks of your child having INFANRIX®-IPV against the expected benefits.

If you have any concerns about your child receiving INFANRIX®-IPV talk to your doctor, nurse or pharmacist.

Keep this leaflet with this vaccine. You may need to read it again

WHAT INFANRIX®-IPV IS USED FOR

INFANRIX®-IPV is a vaccine used in infants from 6 weeks of age and over to prevent four diseases, diphtheria, tetanus, pertussis (whooping cough) and poliomyelitis (polio). The vaccine works by causing the body to produce its own protection (antibodies) against these diseases.

Diphtheria, tetanus, and pertussis are all serious life-threatening diseases caused by bacterial infection. Poliomyelitis is an infectious diseases caused by viral infection.

Diphtheria
Diphtheria mainly affects the airways and sometimes the skin. Generally the airways become inflamed (swollen) causing severe breathing difficulties and sometimes suffocation. The bacteria also release a toxin (poison), which can cause nerve damage, heart problems, and death. The risk of serious complications and death is greater in the very young and elderly.

Tetanus (Lockjaw)
Tetanus bacteria enter the body through wounded skin. Wounds that are especially prone to infection are burns, fractures, deep wounds or wounds contaminated with soil, dust, horse manure or wood splinters. The bacteria release a toxin (poison), which can cause muscle stiffness, painful muscle spasms, fits and death. The spasms can be strong enough to cause bone fractures of the spine. The death rate is 30-40% of cases.

Pertussis (Whooping cough)
Pertussis is a highly infectious illness. The disease affects the breathing tract causing severe spells of coughing that may interfere with normal breathing. The coughing is often accompanied by a 'whooping' sound. The cough may last for 1-2 months or longer. Pertussis can also cause inner ear infections, long-lasting bronchitis, pneumonia, fits, brain damage and death. The risk of severe complications and death is greatest in infants under 6 months of age. The death rate is 0.5% for infants under 6 months of age.

Poliomyelitis (Polio)
Polio is a viral infection that can have variable effects. Often it causes only a mild illness but in some people it causes permanent injury or death.

In its severest form, polio infection causes paralysis of the muscles, including those needed for breathing and walking. Polio infection can leave a person unable to breathe without the help of an iron lung machine, unable to walk without leg braces, or confined to a wheel chair. The limbs affected by the disease may be painfully deformed.

Vaccination is the best way to protect against these diseases. INFANRIX®-IPV vaccine cannot give your child diphtheria, tetanus, pertussis or polio infection. The vaccine will not protect against diseases caused by other types of bacteria, viruses or organisms.

BEFORE VACCINATION

INFANRIX®-IPV SHOULD NOT BE GIVEN IF:

- your child has had an allergic reaction to INFANRIX®-IPV, or any ingredient contained in this vaccine. The ingredients in INFANRIX®-IPV are listed at the end of this leaflet. Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.

  If your child had INFANRIX®-IPV before and became unwell, tell your doctor, nurse or pharmacist before the next dose is given.

- your child experienced a disease of the brain within 7 days after previous vaccination with a pertussis containing vaccine.
- your child has had an allergic reaction to any other diphtheria, tetanus, pertussis or inactivated polio containing vaccine (such as Infanrix®, Triple Antigen™, Tripacel™ or IPOL™ vaccine).
- your child has a severe infection with a high temperature. A minor infection such as a cold should not be a problem, but talk to your doctor or nurse about this before vaccination.
- the expiry date printed on the pack has passed.
- the packaging is torn or shows signs of tampering.

If you are not sure whether your child should have INFANRIX®-IPV vaccine, talk to your doctor or nurse. Do not give this vaccine to anyone else; your doctor has prescribed it specifically for your child.

BEFORE INFANRIX®-IPV IS GIVEN TELL YOUR DOCTOR OR NURSE IF:

- your child has any medical problems such as:
  - brain disease or central nervous system (CNS) disease (ie. epilepsy etc.)
  - a bleeding problem or bruises easily
  - lowered immunity due to medical treatment or a medical condition
  - a tendency to febrile convulsions (seizures/fits due to a fever or high body temperature)
  - a family history of Sudden Infant Death Syndrome (SIDS)
  - allergy to the antibiotics: neomycin sulfate and polymyxin sulfate.
- after having INFANRIX®-IPV or another pertussis-containing vaccine (such as INFANRIX® or Triple Antigen™) your child had any problems, especially:
  - a high temperature (40.5°C) within 2 days of vaccination
  - a collapse or shock-like state within 2 days of vaccination
  - crying lasting 3 hours or more within 2 days of vaccination
  - convulsions (seizures/fits) with or without a fever within 3 days of vaccination
- your child has allergies to any other medicines or substances, such as dyes, foods or preservatives

TAKING OTHER MEDICINES

Tell your doctor or nurse if your child is having any prescription or OTC (over-the-counter) medicines. In particular, mention if your child is being given medicines which suppress the immune system, such as high-dose steroids.

Some vaccines may be affected by other medicines. Your doctor, nurse or pharmacist will be able to tell you what to do if INFANRIX®-IPV is to be given with another medicine.

HAVING OTHER VACCINES

Tell your doctor or nurse if your child has received another vaccine recently.

Some vaccines may be affected by other vaccines. Your doctor, nurse or pharmacist will be able to tell you what to do if INFANRIX®-IPV is to be given with another vaccine.

HOW INFANRIX®-IPV IS GIVEN

The doctor or nurse will give INFANRIX®-IPV as an injection. **If you have any concerns about how this vaccine is to be given, talk to your doctor, nurse or pharmacist.**

HOW MUCH IS GIVEN

The dose of INFANRIX®-IPV is 0.5mL.

HOW IT IS GIVEN

INFANRIX®-IPV will be injected into the upper leg muscle in infants under 12 months of age. In children over 12 months of age the injection may be given in the upper arm muscle instead. Each dose of INFANRIX®-IPV is for single use only. Any residual vaccine must be discarded.

The vaccine should never be given intravenously.

WHEN IT IS GIVEN

INFANRIX®-IPV is usually given as a total of three doses as follows:

- First dose: 2 months of age
- Second dose: 4 months of age
- Third dose: 6 months of age

Each dose is given on a separate visit. INFANRIX®-IPV should not be given at birth.

It is also recommended that children up to 6 years of age receive a single booster (follow up) dose of INFANRIX®-IPV.

It is important to return at the recommended times for follow up doses.

You should discuss with your doctor what is needed for your child.

IF A DOSE IS MISSED

If your child misses a scheduled dose, talk to your doctor or nurse and arrange another visit as soon as possible.

WHILE USING INFANRIX®-IPV

THINGS YOU MUST DO:

Keep your child's follow up visits with the doctor or clinic. It is important the follow-up doses of INFANRIX®-IPV are given at the correct times. This will ensure the best effect of the vaccine in protecting your child against diphtheria, tetanus, pertussis and poliovirus infection.

SIDE EFFECTS

Tell your doctor or nurse as soon as possible if your child does not feel or look well during or after having had a dose of INFANRIX®-IPV vaccine.

INFANRIX®-IPV helps protect most children from diphtheria, tetanus, pertussis and poliovirus infection, but it may have unwanted side effects in a few children. All medicines and vaccines can have side effects. Sometimes they are serious; most of the time they are not. Some side effects may need medical treatment. The chance of your child having a serious side effect is very much less than the chance of your child having a permanent injury from the natural infections.

Ask your doctor, nurse or pharmacist to answer any questions you may have.

Most unwanted effects with INFANRIX®-IPV are mild and usually clear up within a few days. These effects, as with other vaccines, generally occur around the injection site.

MILD EFFECTS

- **Tell your doctor if your child has any of the following that are troublesome or ongoing:**
  - pain, redness, swelling, a hard lump around the injection site
  - fever between 38°C and 39.5°C, generally feeling unwell, runny nose or loss of appetite
  - unusual crying (for more than 1 hour), nausea, vomiting, diarrhoea, headache
  - sleepiness, tiredness, nervousness, restlessness, fussiness or difficulty sleeping
  - skin rash, bruising, or purple or red-brown spots visible through the skin (purpura)

MORE SERIOUS EFFECTS

- **Tell your doctor immediately if you notice any of the following:**
  - fever greater than 39.5°C
  - crying for 3 hours or more
  - collapse, or periods of unconsciousness or lack of awareness
  - seizures (convulsions) or fits
- **Contact your doctor immediately or take your child to the casualty department of your nearest hospital if any of the following happens:**
  - sudden sign of allergy such as rash, itching or hives on the skin, swelling of limbs, face, eyes, lips, mouth, throat or other part of the body

- shortness of breath, breathing or swallowing difficulties
- unusual tiredness or weakness that is sudden and severe

These are signs of an allergic reaction. As with all vaccines given by injection there is a very small risk of such reactions. Allergy to INFANRIX®-IPV vaccine is rare. Any such severe reactions will usually occur within the first few hours of vaccination.

- **Other events reported after INFANRIX®-IPV vaccination, but not necessarily related to the vaccine include:**

- coughing, respiratory infections, bronchitis or viral
- infection of the middle ear that may cause earache and temporary hearing loss
- toothache, sore throat

Other side effects not listed above, can also occur during or soon after a dose of INFANRIX®-IPV. **Check with your doctor or nurse if your child has any other effects.**

Do not be alarmed by this list of possible side effects. Your child may not experience any of them.

STORAGE

INFANRIX®-IPV vaccine is usually stored at the doctor's clinic or surgery, or at the pharmacy. But if you need to store INFANRIX®-IPV always:

- Keep INFANRIX®-IPV in the refrigerator stored between +2°C and +8°C. **THE PACK SHOULD NEVER BE FROZEN. FREEZING DESTROYS THE VACCINE.**
- Keep the vaccine out of the reach of children.
- INFANRIX®-IPV should be used immediately after opening.
- Keep INFANRIX®-IPV in the original pack until it is time for it to be given.

PRODUCT DESCRIPTION

WHAT IT LOOKS LIKE

INFANRIX®-IPV comes in a prefilled syringe. It is a white, slightly milky liquid.

INGREDIENTS

The active ingredients of INFANRIX®-IPV are non-infectious substances from tetanus, diphtheria bacteria, purified proteins of pertussis bacteria and inactivated poliovirus. **The vaccine cannot cause these diseases.** Each 0.5mL dose contains:

- 30IU (25Lf U) of diphtheria toxoid
- 40IU (10Lf U) of tetanus toxoid
- 25mcg of pertussis toxoid, 25mcg of filamentous haemagglutinin and 8mcg of 69 kilodalton outer membrane protein (pertactin)
- 40 D-antigen units of poliovirus Type 1, 8 D-antigen units of poliovirus Type 2 and 32 D-antigen units of poliovirus Type 3

The inactive ingredients in the vaccine are: aluminium hydroxide, phenoxyethanol, sodium chloride (salt), polysorbate 80, neomycin (traces), polymyxin (traces), and water.

The manufacture of this product includes exposure to bovine derived materials. No evidence exists that any case of vCJD (considered to be the human form of bovine spongiform encephalopathy) has resulted from the administration of any vaccine product.

FURTHER INFORMATION

INFANRIX®-IPV is only available if prescribed by a doctor.

INFANRIX®-IPV comes in a prefilled syringe (AUST R 80847) or as a glass vial* (AUST R 80848)

MANUFACTURER

GlaxoSmithKline Beecham Biologicals
Rue de l'Institut 89,
1330 Rixensart, Belgium.

DISTRIBUTED IN AUSTRALIA BY

GlaxoSmithKline Australia Pty Ltd
1061 Mountain Highway
Boronia VIC 3155

Date of Preparation:
12 November 2003

* The vial presentation is not currently marketed in Australia.

INFANRIX Consumer Medicine Information

INFANRIX®

Diphtheria-tetanus-acellular pertussis (DTPa) vaccine

CONSUMER MEDICINE INFORMATION LEAFLET

WHAT IS IN THIS LEAFLET

This leaflet answers some of the common questions about INFANRIX vaccine. It does not contain all the available information. It does not take the place of talking to your doctor, nurse or pharmacist.

All medicines and vaccines have risks and benefits. Your doctor has weighed the possible risks of your child having INFANRIX against the expected benefits.

If you have any concerns about your child receiving INFANRIX talk to your doctor, nurse or pharmacist.

Keep this leaflet with this vaccine. You may need to read it again

WHAT INFANRIX IS USED FOR

INFANRIX is a vaccine used to prevent three diseases, diphtheria, tetanus, and pertussis (whooping cough). The vaccine is sometimes called DTPa vaccine.

Diphtheria, tetanus, and pertussis are all serious life-threatening diseases caused by bacterial infection. The vaccine works by causing the body to produce its own protection (antibodies) against these diseases.

Diphtheria
Diphtheria mainly affects the airways and sometimes the skin. Generally the airways become inflamed (swollen) causing severe breathing difficulties and sometimes suffocation. The bacteria also release a toxin (poison), which can cause nerve damage, heart problems, and death. The risk of serious complications and death is greater in the very young and elderly.

Tetanus (Lockjaw)
Tetanus bacteria enter the body through wounded skin. Wounds that are especially prone to infection are burns, fractures, deep wounds or wounds contaminated with soil, dust, horse manure or wood splinters. The bacteria release a toxin (poison), which can cause muscle stiffness, painful muscle spasms, fits and death. The spasms can be strong enough to cause bone fractures of the spine. The death rate is 30-40% of cases.

Pertussis (Whooping cough)
Pertussis is a highly infectious illness. The disease affects the breathing tract causing severe spells of coughing that may interfere with normal breathing. The coughing is often accompanied by a 'whooping' sound. The cough may last for 1-2 months or longer. Pertussis can also cause inner ear infections, long-lasting bronchitis, pneumonia, fits, brain damage and death. The risk of severe complications and death is greatest in infants under 6 months of age. The death rate is 0.5% for infants under 6 months of age.

Vaccination is the best way to protect against these three diseases. INFANRIX vaccine cannot give your child diphtheria, tetanus, or pertussis infection. The vaccine will not protect against diseases caused by other types of bacteria or organisms.

BEFORE VACCINATION

INFANRIX SHOULD NOT BE GIVEN IF :

- your child has had an allergic reaction to INFANRIX, or any ingredient contained in this vaccine. The ingredients in INFANRIX are listed at the end of this leaflet. Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.

  If your child had INFANRIX before and became unwell, tell your doctor, nurse or pharmacist before the first dose is given.
- your child has had an allergic reaction to any other diphtheria, tetanus, pertussis vaccine (such as Triple Antigen vaccine)
- your child experienced a disease of the brain within 7 days after previous vaccination with a pertussis containing vaccine
- your child has a severe infection with a high temperature. A minor infection such as a cold should not be a problem, but talk to your doctor or nurse about this before vaccination

- the expiry date printed on the pack has passed
- the packaging is torn or shows signs of tampering

If you are not sure whether your child should have INFANRIX, talk to your doctor or nurse. Do not give this vaccine to anyone else; your doctor has prescribed it specifically for your child.

BEFORE INFANRIX IS GIVEN TELL YOUR DOCTOR OR NURSE IF:

- your child has any medical problems such as:
  - ♦ brain disease or central nervous system (CNS) disease (ie epilepsy etc)
  - ♦ a bleeding problem or bruises easily
  - ♦ lowered immunity due to medical treatment or a medical condition
  - ♦ a tendency to febrile convulsions (seizures/fits due to a fever or high body temperature)
- after having INFANRIX or diphtheria, tetanus, pertussis vaccination (such as Triple Antigen) your child had any problems, especially:
  - ♦ a high temperature (over 40.5°C) within 2 days of vaccination
  - ♦ a collapse or shock-like state within 2 days of vaccination
  - ♦ crying lasting 3 hours or more within 2 days of vaccination
  - ♦ convulsions (seizures/fits) with or without a fever within 3 days of vaccination
- your child has allergies to any other medicines or substances, such as dyes, foods or preservatives
- your child has received another vaccine recently, or is having any prescription or OTC (over-the-counter) medicines. In particular mention if your child is being given medicines which suppress the immune system, such as high-dose steroids.
- you are or think you may be pregnant or if you intend to become pregnant. Your doctor will discuss with you the possible risks and benefits of receiving INFANRIX during pregnancy
- you are breast feeding. It is not known if INFANRIX passes into breast milk

Some vaccines may be affected by other vaccines or medicines. Your doctor, nurse or pharmacist will be able to tell you what to do if INFANRIX is to be given with another vaccine or medicine.

HOW INFANRIX IS GIVEN

The doctor or nurse will give INFANRIX as an injection. **If you have any concerns about how this vaccine is to be given, talk to your doctor, nurse or pharmacist.**

HOW MUCH IS GIVEN

The dose of INFANRIX is 0.5mL.

HOW IT IS GIVEN

INFANRIX will be injected into the upper leg muscle in infants under 12 months of age. In children over 12 months of age the injection will be given in the upper arm muscle. For infants and children with bleeding problems, the dose may need to be given under the skin (subcutaneously).

The vaccine should never be given intravenously.

WHEN IT IS GIVEN

INFANRIX is generally given as a total of five doses. Each dose is given on a separate visit. The first dose of INFANRIX is given at 2 months of age. The second and third doses are given every 2 months, at 4 and 6 months of age. The fourth dose is given at 18 months of age, and a fifth dose is given at 4 to 5 years of age (before or when your child starts school).

- First dose: 2 months of age
- Second dose: 4 months of age
- Third dose: 6 months of age
- Fourth dose: 18 months of age
- Fifth dose: 4-5 years of age (or before starting school)

It is important to return at the recommended times for follow up doses.

INFANRIX can be used for the fourth and/or fifth doses of DTP (diphtheria tetanus & pertussis) vaccine, in children previously given 3 doses of another brand of vaccine (such as Triple Antigen).

IF A DOSE IS MISSED

If your child misses a scheduled dose, talk to your doctor or nurse and arrange another visit as soon as possible.

WHILE USING INFANRIX

THINGS YOU MUST DO:

Keep your child's follow up visits with the doctor or clinic. It is important the follow-up doses of INFANRIX are given at the correct times. This will ensure the best effect of the vaccine in protecting your child against diphtheria, tetanus, and pertussis infection.

SIDE EFFECTS

Tell your doctor or nurse as soon as possible if your child does not feel or look well during or after having had a dose of INFANRIX.

INFANRIX helps protect most children from diphtheria, tetanus, and pertussis infection, but it may have unwanted side effects in a few children. All medicines and vaccines can have side effects. Sometimes they are serious; most of the time they are not. Some side effects may need medical treatment. The chance of your child having a serious side effect is very much less than the chance of your child having a permanent injury from the natural infections.

Ask your doctor, nurse or pharmacist to answer any questions you may have.

Most unwanted effects with INFANRIX are mild and usually clear up within a few days. These effects, as with other vaccines, generally occur around the injection site.

MILD EFFECTS

- **Tell your doctor if your child has any of the following that are troublesome or ongoing:**
  - pain, redness, swelling, a hard lump, bruising or itching around the injection site
  - fever between 38°C and 40°C
  - restlessness, unusual crying (for more than 1 hour), vomiting, constipation or diarrhoea
  - sleepiness, sleeping longer or disturbed sleep
  - eating or drinking less
  - skin rash

MORE SERIOUS EFFECTS THAT MAY OCCUR RARELY

- **Contact your doctor immediately or take your child to the casualty department of your nearest hospital if any of the following happens:**
  - swelling of limbs, face, eyes, inside of nose, mouth or throat
  - shortness of breath, breathing or swallowing difficulties
  - hives, itching (especially of the hands or feet), reddening of skin (especially around the ears), or severe skin reactions
  - unusual tiredness or weakness that is sudden and severe

These are signs of an allergic reaction. As with all vaccines given by injection there is a very small risk of such reactions. Allergy to INFANRIX is rare. Any such severe reactions will usually occur within the first few hours of vaccination.

  - crying for 3 hours or more
  - collapse, or periods of unconsciousness or lack of awareness
  - seizures (convulsions) or fits
  - fever over 40°C

- **Other events reported after INFANRIX vaccination, but not be necessarily related to the vaccine include:**
  - respiratory infections, viral and middle ear infections.

Other side effects not listed above, can also occur during or soon after a dose of INFANRIX. **Check with your doctor or nurse if your child has any other effects.**

Do not be alarmed by this list of possible side effects. Your child may not experience any of them.

STORAGE

INFANRIX is usually stored at the doctor's clinic or surgery, or at the pharmacy. But if you need to store INFANRIX always:

- Keep INFANRIX in the refrigerator stored between +2°C and +8°C. **THE PACK SHOULD NEVER BE FROZEN. FREEZING DESTROYS THE VACCINE.**
- Keep the vaccine out of the reach of children.
- Keep INFANRIX in the original pack until it is time for it to be given.

Ask your pharmacist what to do with any left over INFANRIX that has expired or has not been used.

PRODUCT DESCRIPTION

WHAT IT LOOKS LIKE

INFANRIX comes in glass vials and prefilled syringes. It is a white, slightly milky liquid.

INGREDIENTS

The active ingredients of INFANRIX are non-infectious substances from tetanus, diphtheria bacteria and purified proteins of pertussis bacteria. **The vaccine cannot cause these diseases.** Each 0.5mL dose contains:

- 30 IU (25Lf) of diphtheria toxoid
- 40 IU (10Lf) of tetanus toxoid
- 25mcg of pertussis toxoid, 25mcg of filamentous haemagglutinin and 8mcg of pertactin.

The inactive ingredients in the vaccine are: aluminium hydroxide, 2-phenoxyethanol, sodium chloride (salt) and water.

The manufacture of this product includes exposure to bovine derived materials. No evidence exists that any case of vCJD (considered to be the human form of bovine spongiform encephalopathy) has resulted from the administration of any vaccine product.

FURTHER INFORMATION

INFANRIX is only available if prescribed by a doctor.

INFANRIX comes in a glass vial (AUST R 54084) or as a prefilled syringe (AUST R 54085)

MANUFACTURER

GlaxoSmithKline Biologicals s.a.
rue de l'Institut 89,
1330 Rixensart, Belgium.

DISTRIBUTED IN AUSTRALIA BY

GlaxoSmithKline Australia Pty Ltd
1061 Mountain Highway
Boronia 3155 VIC

Date of Preparation:
11 November 2003

INFANRIX-HIB Consumer Medicine Information

INFANRIX™-Hib

Diphtheria-tetanus-acellular pertussis (DTPa) and *Haemophilus influenzae* type b (Hib) vaccine

CONSUMER MEDICINE INFORMATION LEAFLET

WHAT IS IN THIS LEAFLET

This leaflet answers some of the common questions about INFANRIX-Hib vaccine. It does not contain all the available information. It does not take the place of talking to your doctor, nurse or pharmacist.

All medicines and vaccines have risks and benefits. Your doctor has weighed the possible risks of your child having INFANRIX-Hib against the expected benefits.

If you have any concerns about your child receiving INFANRIX-Hib talk to your doctor, nurse or pharmacist.

Keep this leaflet with this vaccine. You may need to read it again.

WHAT INFANRIX-Hib IS USED FOR

INFANRIX-Hib is a combination vaccine used in infants to prevent diphtheria, tetanus, pertussis (whooping cough), and *Haemophilus influenzae* type b (Hib) infection. It is only used as a booster for a child who has received the full primary course of Hib vaccination.

Diphtheria, tetanus, pertussis, and Hib are all serious life-threatening diseases caused by bacterial infection. INFANRIX-Hib works by causing the body to produce its own protection (antibodies) against these diseases.

Diphtheria
Diphtheria mainly affects the breathing tract and sometimes the skin. Generally the breathing tract becomes inflamed (swollen) causing severe breathing difficulties and sometimes suffocation. The bacteria also release a toxin (poison), which can cause nerve damage, heart problems, and death. The risk of serious complications and death is greater in the very young and elderly.

Tetanus (Lockjaw)
Tetanus bacteria enter the body through wounded skin. Wounds that are especially prone to infection are burns, fractures, deep wounds or wounds contaminated with soil, dust, horse manure or wood splinters. The bacteria release a toxin (poison), which can cause muscle stiffness, painful muscle spasms, fits and death. The spasms can be strong enough to cause bone fractures of the spine. The death rate is 30-40% of cases.

Pertussis (Whooping cough)
Pertussis is a highly infectious illness. The disease affects the breathing tract causing severe spells of coughing that may interfere with normal breathing. The coughing is often accompanied by a 'whooping' sound. The cough may last for 1-2 months or longer. Pertussis can also cause inner ear infections, long-lasting bronchitis, pneumonia, fits, brain damage and death. The risk of severe complications and death is greatest in infants under 6 months of age. The death rate is 0.5% for infants under 6 months of age.

***Haemophilus influenzae* type b (Hib)**
Hib most frequently causes brain inflammation (swelling), which is generally seen in infants under 18 months of age. The death rate is 5-10% of infants in this age group. In 15-30% of surviving infants there will be some type of serious complication such as: mental retardation, cerebral palsy, deafness, epilepsy or partial blindness. Hib also causes inflammation of the throat, which is mostly seen in children over 18 months of age. It occasionally causes death by suffocation. Less commonly, the bacteria can also infect the blood, heart, lungs, bones, joints, and tissues of the eyes and mouth.

Vaccination is the best way to protect against these four diseases. INFANRIX-Hib vaccine cannot give your child diphtheria, tetanus, pertussis or Hib infection. The vaccine will not protect against diseases caused by other types of bacteria or organisms.

BEFORE VACCINATION

INFANRIX-Hib SHOULD NOT BE GIVEN IF :

- your child has had an allergic reaction to INFANRIX-Hib, or any ingredient contained in this vaccine. The ingredients are listed at the end of this leaflet. Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.

  If your child had INFANRIX-Hib before and became unwell, tell your doctor, nurse or pharmacist before the first dose is given.

- your child has had an allergic reaction to any other diphtheria, tetanus, pertussis vaccine (such as Triple antigen) or *Haemophilus influenzae* type b vaccine.
- your child experienced a disease of the brain within 7 days after previous vaccination with a pertussis containing vaccine
- your child has a severe infection with a high temperature. A minor infection such as a cold should not be a problem, but talk to your doctor or nurse about this before vaccination.
- the expiry date printed on the pack has passed.
- the packaging is torn or shows signs of tampering.

If you are not sure whether your child should have INFANRIX-Hib , talk to your doctor or nurse. Do not give this vaccine to anyone else; your doctor has prescribed it specifically for your child.

INFANRIX-Hib vaccination is not considered necessary for adults and children over 5 years of age.

BEFORE INFANRIX-Hib IS GIVEN TELL YOUR DOCTOR OR NURSE IF:

- your child has any medical problems such as:
  - brain disease or central nervous system (CNS) disease (ie epilepsy etc)
  - a bleeding problem or bruises easily
  - lowered immunity due to medical treatment or a medical condition
  - a tendency to febrile convulsions (seizures/fits due to a fever or high body temperature)

- after having INFANRIX-Hib or diphtheria, tetanus, or pertussis vaccination (such as Triple antigen) your child had any problems, especially:

- a high temperature (over 40.5°C) within 2 days of vaccination
- a collapse or shock-like state within 2 days of vaccination
- crying lasting 3 hours or more within 2 days of vaccination
- convulsions (seizures/fits) with or without a fever within 3 days of vaccination

- your child has allergies to any other medicines or substances, such as dyes, foods or preservatives.

- your child has received another vaccine recently, or is having any prescription or OTC (over-the-counter) medicines. In particular mention if your child is being given medicines which suppress the immune system, such as high-dose steroids.

Some vaccines may be affected by other vaccines or medicines. Your doctor, nurse or pharmacist will be able to tell you what to do if INFANRIX-Hib is to be given with another vaccine or medicine.

HOW INFANRIX-Hib IS GIVEN

The doctor or nurse will give INFANRIX-Hib as an injection. **If you have any concerns about how this vaccine is to be given, talk to your doctor, nurse or pharmacist.**

HOW MUCH IS GIVEN
The dose of INFANRIX-Hib is 0.5mL.

HOW IS IT GIVEN
INFANRIX-Hib will be injected into the upper arm muscle. For some children with bleeding problems, the dose may need to be given under the skin (subcutaneously).

The vaccine should never to given intravenously.

HOW LONG WILL IT BE GIVEN
Infanrix-Hib is only used as a booster for a child who has received the full primary course of Hib vaccination. INFANRIX-Hib is generally given as a booster (one injection) when a child is 18 months of age.

IF A DOSE IS MISSED
If your child misses a scheduled dose, talk to your doctor or nurse and arrange another visit as soon as possible.

WHILE USING INFANRIX-Hib

THINGS YOU MUST DO:
Keep your child's follow up visits with the doctor or clinic. It is important the follow-up doses of INFANRIX-Hib are given at the correct times. This will ensure the best effect of the vaccine in protecting your child against diphtheria, tetanus, pertussis and Hib infection.

SIDE EFFECTS

Tell your doctor or nurse as soon as possible if your child does not feel or look well during or after having had a dose of INFANRIX-Hib .

INFANRIX-Hib helps protect most children from diphtheria, tetanus, pertussis and Hib infection, but it may have unwanted side effects in a few children . All medicines and vaccines can have side effects. Sometimes they are serious; most of the time they are not. The chance of your child having a serious side effect is very much less than the chance of your child having a permanent injury from one of these illnesses. Some side effects may need medical treatment.

Ask your doctor, nurse or pharmacist to answer any questions you may have.

Most unwanted effects with INFANRIX-Hib are mild and usually clear up within a few days. These effects, as with other vaccines, generally occur around the injection site.

MILD EFFECTS

- **Tell your doctor if your child has any of the following that are troublesome or ongoing:**
  - pain, redness, swelling, a hard lump, bruising or itching around the injection site
  - restlessness, loss of appetite, unusual crying (for more than 1 hour), vomiting, or diarrhoea
  - fever (less than 38°C)

MORE SERIOUS EFFECTS THAT MAY OCCUR RARELY

- **As with all vaccines given by injection there is a very small risk of serious allergic reaction. Contact your doctor immediately or take your child to the casualty department of your nearest hospital if any of the following happens:**

  - swelling of limbs, face, eyes, inside of nose, mouth or throat
  - shortness of breath, breathing or swallowing difficulties
  - hives, itching (especially of the hands or feet), reddening of skin (especially around the ears), or severe skin reactions
  - unusual tiredness or weakness that is sudden and severe

  Allergy to INFANRIX-Hib is rare. Any such severe reactions will usually occur within the first few hours of vaccination.

- **Some reactions have been reported rarely after vaccination with INFANRIX-Hib. Contact your doctor immediately or take your child to the casualty department of your nearest hospital if any of the following happens:**

  - collapse, or periods of unconsciousness or lack of awareness
  - seizures or fits

  Some reactions have been reported rarely after vaccination with other diphtheria-tetanus-pertussis vaccines, but not after INFANRIX-Hib. However, contact your doctor immediately or take your child to the casualty department of your nearest hospital if any of the following happens:

  - crying for 3 hours or more
  - fever (of 40.5°C or more)

- **Other events reported after INFANRIX-Hib vaccination, but not be necessarily related to the vaccine include:**
    - breathing tract infections and inflammation (swelling), viral and inner ear infections, and conjunctivitis (eye inflammation)

Other side effects not listed above, can also occur during or soon after a dose of INFANRIX-Hib . **Check with your doctor or nurse if your child has any other effects.**

Do not be alarmed by this list of possible side effects. Your child may not experience any of them.

STORAGE

INFANRIX-Hib is usually stored at the doctor's clinic or surgery, or at the pharmacy. But if you need to store INFANRIX-Hib always:

- Keep INFANRIX-Hib in the refrigerator stored between +2°C and +8°C. **THE PACK SHOULD NEVER BE FROZEN. FREEZING DESTROYS THE VACCINE.**

- Keep the vaccine out of the reach of children.

- Keep INFANRIX-Hib in the original pack until it is time for it to be given.

Ask your pharmacist what to do with any left over INFANRIX-Hib that has expired or has not been used.

PRODUCT DESCRIPTION

WHAT IT LOOKS LIKE

INFANRIX-Hib comes in two parts: the DTPa vaccine is a white, milky liquid (0.5mL) in a glass vial or prefilled syringe, and the Hib vaccine is a white pellet in a glass vial. These parts are mixed together before use.

INGREDIENTS:

The active ingredients of INFANRIX-Hib are non-infectious substances from tetanus, diphtheria bacteria and purified proteins of pertussis bacteria. The extract from *Haemophilus influenzae* type b bacteria is bound to tetanus toxoid. Each 0.5mL dose contains:

- adsorbed diphtheria toxoid 25 Lf
- adsorbed tetanus toxoid 10 Lf
- pertussis toxoid 25mcg, filamentous haemagglutinin 25mcg, pertactin 8mcg and
- purified capsular polysaccharide of Hib 10mcg covalently bound to approximately 30mcg of tetanus toxoid.

The inactive ingredients in the vaccine are: aluminium salts, 2-phenoxyethanol, lactose, sodium chloride (salt), and water.

INFANRIX-Hib does not contain any infectious material.

FURTHER INFORMATION

INFANRIX-Hib is only available if prescribed by a doctor.

INFANRIX-Hib comes in the following:
Monodose packs of 1 DTPa vial (AUST R 67737)
Monodose packs of 1 DTPa prefilled syringe (AUST R 67738)

MANUFACTURER

SmithKline Beecham Biologicals S.A
rue de l'Institut 89,
1330 Rixensart, Belgium.

DISTRIBUTED IN AUSTRALIA BY
SmithKline Beecham Biologicals
SmithKline Beecham (Aust) Pty Ltd
ACN 004 170 932
300 Frankston Rd
Dandenong VIC 3175

Date of Preparation: 25 July, 2000

Category 1 Application for changes to the Product Information
Large swelling reactions
Infanrix®, Infanrix®-Hib, Infanrix®-IPV, Infanrix®-Penta and Infanrix®-hexa

1.3.3. Australian Labelling (mock-ups)

There are no changes proposed to the labels of these products as a result of this application.
Therefore mock-up labels are not required.

[redacted] [redacted] [redacted] [redacted] [redacted]

Document 1

CONFIDENTIAL

Module 1.4 : Information about the Experts

1.4.3 INFORMATION ABOUT THE EXPERT - CLINICAL

According to his/her respective qualifications the undersigned expert declares hereby to have performed the duties set out in the Article 12.2 and in accordance with Annex I, Part I 1.4 of Directive 2001/83/EC, as amended

CLINICAL :

Name of the Expert : s22 [redacted] Signature : s22 [redacted]

Address : GlaxoSmithKline Biologicals
89 rue de l'Institut
B-1330 Rixensart, Belgium

Date : August 05, 2005.

According to the Annex 1 of Directive 2001/83/EC as amended, brief information on the educational background, training and occupational experience is attached.

DocIDREGU [illegible]

s22 [redacted]

PERSONAL INFORMATION

Professional address: GlaxoSmithKline Biologicals
Rue de l'Institut 89
1330 Rixensart
BELGIUM

Phone: s22 [redacted]
Fax:
e-mail: s22 [redacted]@gskbio.com

Date of birth: s22 [redacted]

Citizenship: s22 [redacted]

EDUCATION

s22 [redacted]

PROFESSIONNAL EXPERIENCE

s22 [redacted]

1.5. Specific Requirements for Different Types of Applications

Not Applicable

[redacted]

Category 1 Application for changes to the Product Information
Large swelling reactions
Infanrix®, Infanrix®-Hib, Infanrix®-IPV, Infanrix®-Penta and Infanrix®-hexa

1.6. Confidentiality Statement

Company: GlaxoSmithKline Australia Pty Ltd

All and any information contained in this document is to be regarded as commercial in confidence as it is a trade secret containing unpublished details and results of private research proprietary to GlaxoSmithKline Australia Pty Ltd, the disclosure of which to unauthorised persons (including its competitors) other than in accordance with Section 61 of the Therapeutic Goods Act 1989 (as amended) is prohibited without the express authority of GlaxoSmithKline Australia Pty Ltd.

MANILLA WHITE DIVIDERS 5 TAB A4
marbig
Ref No: 37320
Made in China
www.accobrands.com.au

Category 1 Application for changes to the Product Information
Large swelling reactions
Infanrix®, Infanrix®-Hib, Infanrix®-IPV, Infanrix®-Penta and Infanrix®-hexa

1.7. Statement on availability of Individual Patient Data (IPD)

GlaxoSmithKline Australia Pty Ltd give an assurance that Individual Patient Data for all clinical studies included in this application will be provided upon request, within 15 working days.

1.8. Overseas Regulatory Status

[redacted] [redacted] [redacted]

Category 1 Application for changes to the Product Information
Large swelling reactions
Infanrix®, Infanrix®-Hib, Infanrix®-IPV, Infanrix®-Penta and Infanrix®-hexa

1.8. Overseas Regulatory Status

This application is being submitted simultaneously in all international markets including the EU, Switzerland, Canada and New Zealand.

The supporting data is identical in all markets.

This application has not been rejected or withdrawn in Canada or the US.

Category 1 Application for changes to the Product Information
Large swelling reactions
Infanrix®, Infanrix®-Hib, Infanrix®-IPV, Infanrix®-Penta and Infanrix®-hexa

1.9. Authorisation to refer to Drug and Plasma Master Files

Not Applicable

Category 1 Application for changes to the Product Information
Large swelling reactions
Infanrix®, Infanrix®-Hib, Infanrix®-IPV, Infanrix®-Penta and Infanrix®-hexa

1.10. Summary of Bioavailability Studies

Not Applicable

1.11. GMP Status

[redacted]

Category 1 Application for changes to the Product Information
Large swelling reactions
Infanrix®, Infanrix®-Hib, Infanrix®-IPV, Infanrix®-Penta and Infanrix®-hexa

1.11. GMP Status

This section contains certificates for the following manufacturing sites which are involved in various steps of manufacture for the concerned products. There are no changes proposed to the current manufacturers resulting from this application.

	Site Name & Address	*Enterprise No*
1	GlaxoSmithKline Biologicals SA Rue de L'Institut 89, 1330 Rixensart, Belgium	11492
2	GlaxoSmithKline Biologicals SA Parc De La Noire Epine, Rue Flemming 20-1300, Wavre, Belgium	28615
3	Sachsisches Serumwerk Dresden Div SmithKline Beecham Pharma GMBH & Co KG Zirkusstrasse 40, 01069 Dresden, Germany	21154
4	GlaxoSmithKline Australia Pty Ltd 1061 MountainHighway, Boronia, VIC, 3155, Australia	40010
5	Sigma Pharmaceuticals Pty Ltd 286-302 Frankston-Dandenong Rd, Dandenong South, VIC, 3175	482
6	Chiron Behring GMBH & Co KG Emil-Von-Behring-Strasse 76, 35041, Marburg, Germany	65

Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

s22 [redacted]
GlaxoSmithKline Australia Pty Ltd
PO Box 168
BORONIA VIC 3155
Australia

Sponsor Client ID: 40010

GMP Clearance Application MI-18102004-CL-000047-1 Notification.

I am pleased to advise that GMP Clearance is approved for the following manufacturer and for the type of products indicated below.

GLAXOSMITHKLINE BIOLOGICALS SA
Rue de L'Institut 89
1330 Rixensart
Belgium

Manufacturer Client ID: 11492

Manufacturing Type	Sterility	Dosage Form	Manufacturing Step
Drug Manufacture	Sterile	Small volume parenterals (vaccines)	All steps

This Clearance remains current until 29 November 2007 unless otherwise revoked.

You are advised to submit a new GMP Clearance application with updated GMP evidence prior to the expiry date to avoid delays in the registration/listing of new products and maintain products on the Australian Register of Therapeutic Goods (ARTG). Expired GMP Clearance could result in affected product(s) being removed from the ARTG.

THIS CLEARANCE LETTER SHOULD BE USED FOR FUTURE LISTING/REGISTRATION OF THE PRODUCT TYPES SPECIFIED ABOVE.

Yours sincerely

s22 [redacted]
GMP Clearance Unit
Manufacturer Assessment Section
Office of Devices, Blood & Tissues
6/01/2005

Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

[redacted]
GlaxoSmithKline Australia Pty Ltd
PO Box 168
BORONIA VIC 3155
Australia

Sponsor Client ID: 40010

GMP Clearance Application MI-18102004-CL-000048-1 Notification.

I am pleased to advise that GMP Clearance is approved for the following manufacturer and for the type of products indicated below.

GLAXOSMITHKLINE BIOLOGICALS SA
Parc De La Noire Epine
Rue Flemming 20-1300 Wavre
Belgium

Manufacturer Client ID: 28615

Manufacturing Type	Sterility	Dosage Form	Manufacturing Step
Drug Manufacture	Sterile	Small volume parenterals (vaccines)	All steps

This Clearance remains current until 18 November 2006 unless otherwise revoked.

You are advised to submit a new GMP Clearance application with updated GMP evidence prior to the expiry date to avoid delays in the registration/listing of new products and maintain products on the Australian Register of Therapeutic Goods (ARTG). Expired GMP Clearance could result in affected product(s) being removed from the ARTG.

THIS CLEARANCE LETTER SHOULD BE USED FOR FUTURE LISTING/REGISTRATION OF THE PRODUCT TYPES SPECIFIED ABOVE.

Yours sincerely

s22 [redacted]

GMP Clearance Unit
Manufacturer Assessment Section
Office of Devices, Blood & Tissues
6/01/2005

TGA THERAPEUTIC GOODS ADMINISTRATION
PO Box 100, Woden, ACT 2606, Australia
Telephone: (02)6232 8629. Fax: (02)6232 8426

Attention: [redacted]
GlaxoSmithKline Australia Pty Ltd
PO Box 168
BORONIA VIC 3155

Your application for preclearance has been reviewed.

GMP Reference No: **7899/03**

Manufacturer Enterprise: **21154**

Manufacturer Name:
SACHSISCHES SERUMWERK DRESDEN DIV SMITHKLINE BEECHAM PHARMA GMBH & CO KG

Manufacturer Site Address:
ZIRKUSSTRASSE 40
01069 DRESDEN
GERMANY

Manufacturer Class: **L1**
Manufacturer Type: **DRUG**
Dosage Forms:
N/A-Not applicable

Codes for Steps of manufacture: **ALL**
Qualifying Comments: **VACCINES**

The evidence for GMP Compliance is acceptable.

This remains current until 25 November, 2005 unless otherwise revoked.

You are advised to obtain updated GMP evidence prior to the expiry date to avoid delays in the registration/listing of new products. Failure to provide current acceptable GMP evidence when requested could result in affected product(s) being removed from the Australian Register of Therapeutic Goods.

THIS PRECLEARANCE LETTER SHOULD BE USED FOR FUTURE LISTING/REGISTRATION OF THE PRODUCT TYPE SPECIFIED ABOVE.

s22 [redacted]

GMP Audit & Licensing Section
Conformity Assessment Branch
20 March, 2003
GMP enquiries: Telephone (02) 6232 8629, Fax (02) 6232 8426

Document 1

AUSTRALIA

Commonwealth Department of Health and Ageing

Licence to Manufacture Therapeutic Goods

LICENCE NO: 521

Manufacturer:

GLAXOSMITHKLINE AUSTRALIA PTY LTD ACN 100 162 481

anufacturing site for which the licence applies:

1061 MOUNTAIN HIGHWAY
BORONIA VIC 3155

The above named manufacturer is hereby authorised to carry out the following kind(s) of manufacture:

Manufacture of sterile and non-sterile therapeutic goods for human use.

on the above premises subject to conditions imposed by the Therapeutic Goods Act 1991 and its Regulations and to the additional conditions issued separately and forming part of this licence.

Originally Issued: **05/11/1991** s22 [redacted] Date Revised: **20/04/2005**

s22 [redacted]

Signed: .....[redacted].....

Delegate of the Secretary

Commonwealth Department of Health and Ageing 02783

This licence is the property of the Therapeutic Goods Administration and must be returned upon demand. This licence remains valid until otherwise suspended or revoked by the Therapeutic Goods Administration.

Document 1

Schedule of Conditions Applicable To The Manufacture of Therapeutic Goods

The following conditions apply to and form part of Licence No 521 issued in respect of:

GLAXOSMITHKLINE AUSTRALIA PTY LTD ACN 100 162 481

1061 MOUNTAIN HIGHWAY
BORONIA VIC 3155

under the Therapeutic Goods Act, 1989.

This licence does not authorise the manufacture of therapeutic devices or preparations containing penicillin drugs.

The manufacture of antineoplastic and immunomodulator products is limited to secondary packaging only.

Persons currently nominated as having control under Section 37 of the Therapeutic Goods Act, 1989:

Production: s22 [redacted]

Quality Control:

Originally Issued: **05/11/1991** s22 [redacted] Date Revised: **20/04/2005**

Signed: .....

Delegate of the Secretary

Health and Ageing 02764

This licence is the property of the Therapeutic Goods Administration and must be returned upon demand. This licence remains valid until otherwise suspended or revoked by the Therapeutic Goods Administration.

TGA THERAPEUTIC GOODS ADMINISTRATION

Document 1

AUSTRALIA

Commonwealth Department of Health and Aged Care

Licence to Manufacture Therapeutic Goods

LICENCE NO: **2069**

Manufacturer:

SIGMA PHARMACEUTICALS PTY LTD
ACN: 004 118 594

Manufacturing site for which the licence applies:

See Attachment 1.

The above named manufacturer is hereby authorised to carry out the following kind(s) of manufacture:

Manufacture of sterile and non-sterile therapeutic goods for human use.

on the above premises subject to conditions imposed by the Therapeutic Goods Act 1989 and its Regulations and to the additional conditions issued separately and forming part of this licence.

Originally Issued: [redacted] Date Revised: **04/04/2002**

s22

Signed: ...

Chief GMP Auditor - TGA
Delegate of the Secretary

This licence is the property of the Therapeutic Goods Administration and must be returned upon demand. This licence remains valid until otherwise suspended or revoked by the Therapeutic Goods Administration.

Document 1

Commonwealth Department of Health and Aged Care

Attachment 1 to Licence No. 2069 to Manufacture Therapeutic Goods

Manufacturing sites for which licence applies:

Principal Site:

96 MERRINDALE DRIVE
CROYDON VIC 3136

Additional Sites:

432 MT DANDENONG ROAD
CROYDON VIC 3136

1408 CENTRE ROAD
CLAYTON VIC 3168

286-302 FRANKSTON-DANDENONG RD
DANDENONG SOUTH VIC 3175

Originally Issued: 02/06/1992 Date Revised: 04/04/2002

Signed: s22 [redacted]

Chief GMP Auditor - TGA
Delegate of the Secretary

This licence is the property of the Therapeutic Goods Administration and must be returned upon demand. This licence remains valid until otherwise suspended or revoked by the Therapeutic Goods Administration.

Schedule of Conditions Applicable To The Manufacture of Therapeutic Goods

The following conditions apply to and form part of Licence No 2069 issued in respect of:

SIGMA PHARMACEUTICALS PTY LTD
ACN: 004 118 594
286-302 FRANKSTON-DANDENONG RD
DANDENONG SOUTH VIC 3175

under the Therapeutic Goods Act, 1989.

This licence holder is required to keep records of stability studies for each different therapeutic good which is manufactured on behalf of a separate sponsor unless there is an agreement in writing between the licence holder and the sponsor of each such therapeutic good which specifies this to be the responsibility of the sponsor.

The licence holder is required to keep records of stability studies for each different therapeutic good which is manufactured on its behalf unless there is an agreement in writing between the licence holder and the contract manufacturer of each such therapeutic good which specifies this to be the responsibility of the contract manufacturer.

Persons currently nominated as having control under Section 37 of the Therapeutic Goods Act 1989:

Production: s22 [redacted]

Quality Control:

Originally Issued: 02/06/1992 Date Revised: 04/04/2002

Signed: s22 [redacted]

Chief GMP Auditor - TGA
Delegate of the Secretary

This licence is the property of the Therapeutic Goods Administration and must be returned upon demand. This licence remains valid until otherwise suspended or revoked by the Therapeutic Goods Administration.

Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

18 APR 2005

Attention: [redacted]
GlaxoSmithKline Australia Pty Ltd
PO Box 168
BORONIA VIC 3155

Sponsor Client ID: 40010

GMP Clearance Application MI-22122004-CL-000716-1 Notification.

I am pleased to advise that GMP Clearance is approved for the following manufacturer and for the type of products indicated below.

CHIRON BEHRING GMBH & CO KG
EMIL-VON-BEHRING-STRASSE 76
35041 MARBURG
Germany

Manufacturer Client ID: 65

API Name	Manufacturing Step
Biological Products - Vaccines	Active material manufacture

This Clearance remains current until 16/07/2007 unless otherwise revoked.

You are advised to submit a new GMP Clearance application with updated GMP evidence prior to the expiry date to avoid delays in the registration/listing of new products and maintain products on the Australian Register of Therapeutic Goods (ARTG). Expired GMP Clearance could result in affected product(s) being removed from the ARTG.

THIS CLEARANCE LETTER SHOULD BE USED FOR FUTURE LISTING/REGISTRATION OF THE PRODUCT TYPES SPECIFIED ABOVE.

For further information please refer to the Therapeutic Goods Administration website: http://www.tga.gov.au/manuf/index.htm alternatively you may contact the GMP Clearance Unit on (02) 6232 8946.

Yours sincerely
s22 [redacted]
GMP Clearance Unit
Manufacturer Assessment Section
Office of Devices, Blood & Tissues
13/04/2005

MANILLA
WHITE DIVIDERS
5 TAB A4
marbig
Ref No: 37320
Made in China
www.accobrands.com.au

Category 1 Application for changes to the Product Information
Large swelling reactions
Infanrix®, Infanrix®-Hib, Infanrix®-IPV, Infanrix®-Penta and Infanrix®-hexa

1.12. Provisional ARTG Record (PAR)

As this application is for changes to the Product Information of the Infanrix range of products, the ARTG records have not changed.

Please note that the ARTG SIME entries for all Infanrix products have been validated and corrected as part of the ARTG Update Project. The validated ARTG entries were submitted to TGA between August and October 2004.